PB-218 287

CLINICAL HANDBOOK ON ECONOMIC POISONS; EMERGENCY INFORMANTION FOR TREATING POISONS

Wayland J. Hayes, Jr.

Communicable Disease Center
Atlanta, Georgia

1963

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PB 218 287

CLINICAL HANDBOOK ON ECONOMIC POISONS

Emergency Information for Treating Poisoning

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U. S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
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The U. S. Department of Health, Education, and Welfare, including the Public Health Service, has a vital interest in the entire field of poison control including, but not limited to, the toxicology of pesticides.

The Poison Control Branch of the Division of Accident Prevention, Public Health Service, provides interchange of information for poison control centers throughout the country as a part of its broad poison control activities.

A "Directory of Poison Control Centers," compiled by the Division of Accident Prevention, can be purchased for 20 cents through the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C.

CLINICAL HANDBOOK ON ECONOMIC POISONS

Emergency Information
for Treating Poisoning

WAYLAND J. HAYES, JR., M.D., Ph.D.

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
Communicable Disease Center – Toxicology Section
Atlanta, Georgia
1963

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Names of commercial manufacturers and trade names of pesticides are provided for identification only.

This handbook is a revision of Public Health Service Publication No. 476 originally published in 1956 under the title "Clinical Memoranda of Economic Poisons."

Public Health Service Publication No. 476
Revised 1963

U. S. Government Printing Office, Washington: 1963

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INTRODUCTION

The Toxicology Section of the Technology Branch of the Communicable Disease Center conducts laboratory, field, and clinical studies to determine the toxic hazards to man that are involved in the use of economic poisons in public health and agriculture. The subjects of clinical study include: (1) persons with occupational exposure – including malaria-control spraymen, farmers, orchardists, spray pilots, pest control operators, and others with heavy occupational exposure; (2) volunteers who take part in strictly experimental investigations of pesticides under controlled conditions; and (3) patients who are sick as a result of accidental over-exposure to pesticides. Facilities available for this work include the main laboratory at Atlanta, Georgia, and field stations at Wenatchee, Washington, and Phoenix, Arizona. Special study cases may be admitted to Public Health Service Hospitals in accordance with Division of Hospitals Operations Manual Part B, Chapter 1, Section 21.1, which was issued under authority of Section 301(f), Public Law 410. Additional facilities for the study of volunteers have been made available generously by other institutions.

This Handbook replaces the "Clinical Memoranda on Economic Poisons," which were first issued in March 1950 as separate releases on several new insecticides. Additional compounds were discussed in subsequent editions. No attempt has been made in the Memoranda or in the Handbook to cover a large number of compounds. Attention has been given to those materials that are manufactured in large amounts, that are known to have caused poisoning relatively frequently, or that are of special interest for some other reason. In general, the pesticides introduced before DDT have been omitted because information on them is readily available in textbooks of pharmacology. However, sections have been devoted to arsenic, thallium, phosphorus, and kerosene because they are leading causes of deaths associated with pesticides.

The Handbook is based on research of the Toxicology Section as well as reports from other sources. No credit or reference is given unless it is felt that such a reference is reasonably available to most readers and would be of some real use to the physician in the management of his patient. The Handbook is prepared primarily for the guidance of physicians in the diagnosis and treatment of persons who may have had extensive or intensive exposure to economic poisons; however, it contains general information that may be of interest to others also.

Form of the Handbook

This Handbook is arranged under several main headings such as "Organic Phosphorus Insecticides," "Chlorinated Hydrocarbon Insecticides," and "Rodenticides." In order to conserve space, statements that apply to all members of a class of pesticides have been placed immediately under the main heading for that class and have not been repeated in the sections on the individual compounds. Synonyms for the different pesticides have not been listed in the text, but some are given in the index.

A part of each section is devoted to a description of the chemical nature, formulations, and uses of the compound under consideration. This portion is intentionally a very brief resume of the subject matter and is intended to guide the attending physician in questioning the patient on his exposure to economic poisons or their solvents. It must be understood clearly that, especially for the newer organic poisons, very much more is known now regarding their chemical nature, formulations, and uses than is known about treatment or even the diagnosis of acute or chronic poisoning by them in man.

The remainder of each section is devoted to medical considerations including mode of action, diagnosis, and treatment. This part is developed in greater detail than the first, although it is on these medical considerations that research is most urgently needed. In many instances, the suggestions for treatment are based on general medical principles and on animal experimentation because many of the forms of poisoning have never been observed in man.

Attention is called to the analytical services offered to physicians in connection with cases of poisoning. Directions for the collection and shipping of samples are given as appendices to this Handbook. (Only those samples that cannot be processed adequately by local or State laboratories should be submitted.) Other appendices contain a convenient form for the collection of data in cases of suspected poisoning and directions for giving artificial respiration.

Interpretation of Toxicity

Any compound may be toxic if it is absorbed to an excessive degree. The simplest way of expressing the toxicity of a compound is by means of an LD_{50}-value. Such a value is a statistical estimate of the dosage necessary to kill 50 percent of a very large population of the test species under stated conditions (e.g., single oral dose of aqueous solution).

Caution is necessary in the interpretation of LD_{50}-values.

First, hazards presented by any compound depend more on how it is used than on how toxic it is. In this country, the majority of the fatal and nonfatal accidents caused by solid or liquid substances involve relatively nonpoisonous materials, available to a great number of people and sometimes used with reckless carelessness. This fact does not reduce the tragedy of needless injury. Also, highly toxic substances do present a relatively greater hazard if used under comparable conditions.

Second, it is known that toxicity may vary with species, age, sex, nutritional state, and formulation of poison, as well as with the route of administration. By necessity, LD_{50}-values are given for animals. They can be applied only with reservation to man.

Third, an LD_{50}-value is a statistic which, in itself, gives no information on the dosage that will be fatal to a very small proportion of a large group of animals. Although values such as the

LD_5 or LD_1 may be determined for laboratory animals, they are (for statistical reasons) less precise than the corresponding LD_{50}-value and, therefore, even more difficult to apply to man.

Fourth, LD_{50}-values are usually expressed in terms of single dosages only. Thus, these values give little or no information about the possible cumulative effects of a compound.

In spite of these necessary qualifications, LD_{50}-values are useful in making an objective comparison of the inherent toxicity of different compounds. Some materials are so poisonous that known exposure to a few drops on the skin is reasonable justification for diagnosing consistent illness as poisoning. On the contrary, other compounds are so relatively harmless that a small dose may be ingested without causing any harm. As a very general guide, the probable lethal oral dose for a grown person may be estimated as follows:

Acute oral LD_{50} for any animal (mg./kg.)	**Probable lethal oral dose of technical material for a human adult**
Less than 5	a few drops
5 to 50	"a pinch" to 1 teaspoonful
50 to 500	1 teaspoonful to 2 tablespoonsful
500 to 5,000	1 ounce to 1 pint (1 pound)
5,000 to 15,000	1 pint to 1 quart (2 pounds)

It has been found that occupational poisoning with nonfumigant pesticides shows a very much closer correlation with acute dermal LD_{50}-values than with oral toxicity.

Suggestions for Clinical Study

In certain cases, the life of the patient has been saved because the physician suspected poisoning and began vigorous treatment promptly. Response to therapy may help to establish the diagnosis. However, proof of adequate exposure to a poison should be obtained after the crisis if not before. The compound or a metabolite may be present in the excreta. For at least 24 hours after onset, all vomitus, urine, and feces should be saved systematically.

The history of each case is of the greatest importance. If the fact of exposure to a toxicant is clearly established, it is then necessary to know what poison or poisons were involved (including the solvents and other adjuvants); the concentration and amount of the contaminating material; the type, duration, and frequency of exposure; and the period from exposure to the onset of symptoms. Not only is the most recent exposure important, but all preceding known instances should be listed. To facilitate the taking and recording of an adequate toxicologic history, a form (Appendix A) has been devised and copies are available upon request from the Toxicology Section.

A careful neurologic examination is essential because the syndromes associated with many pesticides are predominantly neurologic.

The physician will perform only those tests and administer only those treatments that he believes are indicated. On the other hand, to learn more about poisoning and treatment, it is desirable to collect comparable data from a number of patients. To that end, it is respectfully requested that the tests listed below be considered and performed if there is no medical or administrative contraindication. Tests that are abnormal should be rechecked to rule out laboratory error. Confirmed abnormalities should be studied in detail. Reports of all tests should include a statement of the method and of the normal range for that test in the laboratory where it was made. Most of the tests suggested are nonspecific in regard to any particular toxicant. Although the clinical manifestations of poisoning in man with many of the newer groups of pesticides are primarily neurologic in origin, repeated dosages of the chlorinated hydrocarbon insecticides may produce pathologic changes in the liver and kidney without signs referable to these organs (as they do under appropriate conditions in experimental animals). For this reason, special attention should be given to liver and kidney function tests in man in order that urgently needed data may be collected with reference to the possible effects of pesticides on these organs in man. The following clinical and laboratory tests are suggested:

- Complete blood count including:
  - Red cell count
  - Reticulocyte count
  - White cell count
  - Differential count
- Hemoglobin (in grams percent)
- Hematocrit
- Urinalysis
- Serologic test for syphilis
- Lumbar puncture with cerebrospinal fluid analysis if there is any neurosymptomatology
- Phenolsulfonphthalein kidney test
  [inject 1.0 ml. (6 mg.) of dye intravenously and collect a specimen of urine every 15 minutes for 2 hours.]
- Mosenthal test
- Nonprotein nitrogen of the blood
- Icterus index
- Urobilin in the urine (Schlesinger's test)
- Bromsulfalein liver function test (inject 5 mg./kg. and make a reading at 45 minutes).
- Cephalin flocculation
- Blood pressure (at least daily)
- X-ray of chest
- Basal metabolic rate (BMR)
- Electrocardiogram
- Electroencephalogram, if equipment is available
- Certain other specific tests (including tissue biopsy or examination of stomach contents, excreta, or blood) listed under "Laboratory Findings" for each particular economic poison. (Directions for taking and shipping biopsy specimens form Appendix B. Directions for preparing and shipping blood samples for

cholinesterase determination form Appendix C. Directions for shipping stomach contents form Appendix D.)

General Suggestions for Treatment

In many cases of poisoning, the nature of the toxic agent is not known. The treatment is, therefore, symptomatic and may include:

(1) Removal of the toxic agent.

(a) Emesis or gastric lavage if poison has been taken internally. As a first aid measure after ingestion of a nonirritant poison, vomiting may be produced by putting a finger down the patient's throat or by giving a child 20 ml. of syrup of ipecac plus water to mobilize the poison. Do not repeat the dose of ipecac as a first aid measure. Never try to make a stuperous or unconscious person vomit. Never use fluid extract of ipecac.

(b) Evacuation of the gut (avoiding oily laxatives where it is possible that an organic solvent or a halogenated insecticide is involved).

(c) Thorough washing of the eyes or body if there has been external contact with the poison.

(d) Removal of the patient to fresh air if poisoning has resulted from exposure to a contaminated atmosphere.

(2) Supportive therapy.

(a) Sedatives. Sodium pentobarbital is preferred for acute poisoning because of its rapidity of action. Phenobarbital is useful in maintaining a prolonged level of sedation to combat persisting hyperexcitability or recurring convulsions.

(b) Stimulants. **In treating vascular collapse, substances such as adrenalin should be used only after careful consideration; these stimulants are contraindicated in poisoning by the halogenated hydrocarbon insecticides, even though the patient may be in severe depression or coma.**

(c) Transfusions. Patients in shock, for whatever reason, may be helped by transfusion unless pulmonary edema or some other contraindication is present. If blood is not readily available or if simple dehydration is present, 5% glucose or normal saline infusions are indicated. Intravenous fluids should not be continued long without a careful laboratory evaluation of the acid-base balance.

(d) Artificial Respiration. (For a suggested method see Appendix E.) It is more important to provide a free respiratory passage and, if necessary, artificial respiration to an anoxic patient than it is to move him to a doctor or hospital. Frequently, the physician is in telephone contact with the patient's family or associates quite early. The physician should inquire about the victim's breathing and color. If anoxia seems to be present or imminent, a warning should be given against moving the patient, and someone trained and equipped for giving emergency mechanical artificial respiration (usually the fire department) should be called. If necessary, the person initiating the telephone call should be instructed in artificial mouth-to-mouth respiration to be carried out while the physician goes to the patient.

(e) Oxygen therapy. Oxygen should be administered to patients showing cyanosis or severe respiratory difficulty. Patients with pulmonary edema require oxygen under positive pressure as well as postural drainage and dehydration therapy until the condition is corrected.

These suggestions for symptomatic treatment are intentionally brief and emphasize early treatment. More detailed information may be found in the following recommended books:

von Oettingen, W.F.: Poisoning, A Guide to Clinical Diagnosis and Treatment, Second Edition, Philadelphia, W.B. Saunders Co., 1958.

Gleason, M.N.; Gosselin, R.E.; and Hodge, H.C Clinical Toxicology of Commercial Products, Acute Poisoning (Home and Farm), Baltimore, Williams and Wilkins Co., 1957.

It is understood that, if the nature of the toxic agent is known, the physician may be able to use a specific antidote to supplement the general treatment. Where an antidote is known, it is described in the section on "Treatment" dealing with each pesticide. In any event, the importance of general medical care in cases of poisoning should not be underestimated. Even when a recognized antidote is properly administered, the general care of the patient may do as much or more to insure his survival.

Additional information on a pesticide frequently may be obtained from the medical department of the company which manufactures the compound in question. For emergency consultation, physicians or hospital representatives may also call the nearer of the following representatives of the Public Health Service:

Dr. Wayland J. Hayes, Jr.	Dr. Griffith E. Quinby
Atlanta, Georgia (AC:404)	Wenatchee, Washington (AC:509)
Office: 634-5131	Office: 662-5506
Home: 373-7158	Home: 663-6175

Reporting

In cases of pesticide poisoning, no matter how mild, physicians and others are urged to notify promptly the nearest of the following laboratories:

Communicable Disease Center
Atlanta 22, Georgia
Attn: Toxicology Section

U. S. Public Health Service
P. O. Box 73
Wenatchee, Washington

U. S. Public Health Service
4402 North Seventh Street
Phoenix 12, Arizona

This direct notification is not to be confused with or intended to be a substitute for the morbidity reports usually sent local and State departments of health or poison control centers.

Reports are solicited not only on cases that involve clearly established poisoning but also on cases that present a diagnostic problem, even after thorough study. However, past experience has shown that the following caution is necessary: Before chronic poisoning is reported, be sure that exposure to a pesticide has occurred.

The narrative report that is requested for each case of poisoning should be more complete than the average clinical summary, for it will frequently be impossible to refer to the original chart. These case histories form one important source of information for this booklet, so that the experience of one person may help many. All information received will be kept confidential so far as the identity of the patient is concerned.

Prevention of Poisoning

In the United States pesticides kill more children than adults. It is probable that nonfatal poisoning also occurs predominantly in children. These cases in children could be virtually eliminated if (a) pesticides were always stored under lock and key, (b) care were taken that children could not reach the poisons while they are in use, and (c) empty containers were disposed of safely. Some of the compounds are extremely persistent. Poisoning has occurred from contact with a cup used a year before for measuring a pesticide.

Strangely enough most deaths caused by pesticides are still associated with arsenic, phosphorus, and other poisons that were available before the introduction of DDT and newer materials. Great care should be used with all poisons – including those that are so familiar that some people forget their undiminished danger.

ORGANIC PHOSPHORUS INSECTICIDES

Introduction: The organic phosphorus insecticides are characterized by (1) similar chemical structure (they may all be considered derivatives of phosphoric acid) and (2) similar primary mode of action. These insecticides differ widely in their inherent toxicity and differ at least to some extent in their rate of absorption, point of maximal action following absorption, and rate of destruction or excretion. The acute oral and dermal LD_{50}-values to rats of certain organic phosphorus insecticides including those mentioned in this Handbook are given in the table on page 13.

Routes of Absorption: Organic phosphorus insecticides are absorbed by the skin as well as by the respiratory and gastrointestinal tracts. Absorption by the skin tends to be slow, but, because the insecticides are difficult to remove, such absorption is frequently prolonged. Skin absorption is somewhat greater at higher temperatures and is much greater in the presence of dermatitis. Thus, dermatitis may lead to serious poisoning following exposure that would ordinarily cause no inconvenience.

Pharmacologic Action: The organic phosphorus poisons act as more or less irreversible inhibitors of the enzyme cholinesterase and thus allow the accumulation of large amounts of acetylcholine. The cholinesterase content of various tissues is not equally affected in the same poisoned animal, and the level in all tissues including even the brain can be lowered markedly from the prepoisoning level without seriously affecting normal function, especially if the reduction is gradual. Almost as important as the degree of cholinesterase depression is the rate at which it occurs. A sudden slight depression resulting from a small dose that is rapidly absorbed may lead to incapacitating acute illness, though not to fatal illness. A sudden marked depression from a sufficient dose leads to critical and frequently fatal poisoning. However, the blood cholinesterase of men and animals may be gradually depressed

ACUTE ORAL AND DERMAL LD_{50}-VALUES OF ORGANIC PHOSPHORUS INSECTICIDES FOR MALE AND FEMALE WHITE RATS*

COMPOUND	ORAL LD_{50} (MG./KG.)		DERMAL LD_{50} (MG./KG.)	
	MALES	FEMALES	MALES	FEMALES
Carbophenothion	30	10.0	54	27
Chlorthion	880	980	< 4500	4100
Co-Ral	41	15.5	860	–
DDVP	80	56	107	75
Delnav	43	23	235	63
Demeton	6.2	2.5	14	8.2
Diazinon	108	76	900	455
Dicapthon	400	330	790	1250
Dimethoate	215	–	400	–
Di-Syston	6.8	2.3	15	6
EPN	36	7.7	230	25
Ethion	65	27	245	62
Fenthion	215	245	330	330
Guthion	13	11	220	220
Malathion	1375	1000	> 4444	> 4444
Methyl parathion	14	24	67	67
Methyl Trithion	98	120	215	190
NPD	–	–	2100	1800
Parathion	13	3.6	21	6.8
Phorate	2.3	1.1	6.2	2.5
Phosdrin	6.1	3.7	4.7	4.2
Phosphamidon	23.5	23.5	143	107
Ronnel	1250	2630	–	–
Schradan	9.1	42	15	44
TEPP	1.05	–	2.4	–
Trichlorofon	630	560	> 2000	> 2000

*With the exception of the dermal LD_{50} for dimethoate, these values were determined by the Toxicology Section under standardized conditions.

to a very low level (<0.2 Δ ph/hr in man) by repeated small exposures to organic phosphorus compounds without necessarily producing serious symptoms or even any symptoms whatever. Thus, a very low blood cholinesterase is not always proof that a clinical illness represents poisoning, but critical poisoning usually does not occur in man or laboratory animals in the absence of such enzyme levels. In every case, the exposure history, symptoms, and clinical findings must be considered carefully, no matter what the cholinesterase level may be.

It is known now that some effects of organic phosphorus insecticides (e.g., headache and irritation of the urinary tract both caused by paranitrophenol) are not always related directly to the inhibition of cholinesterase, but the relative importance of different processes in determining the clinical outcome is not established. In any event, recovery is apparently complete if a poisoned animal or man has time to re-form his critical quota of cholinesterase. Experiments with rats show that gradual depression of the blood cholinesterase by repeated, small, tolerated doses does not make the animals significantly more susceptible to a challenge dose. Field experience suggests that the same is true of man. Thus, there is a physiological adjustment to the stress of repeated, small, tolerated doses that is at least partially independent of the blood cholinesterase *per se*. On the contrary, repeated doses which produce any detectable clinical injury in rats tend not only to reduce cholinesterase levels progressively but to produce cumulative clinical injury also. Thus, if a small second dose of poison is administered before physiological adjustment is complete, the effect is partially additive. Following clinical recovery after illness caused by one or a few doses, physiological adjustment may be safely presumed complete only after the activity of the blood cholinesterases has returned to normal. Depending on the degree of depression and other factors, the recovery may require about three months. This does not mean that workers who have been poisoned may not return to work much sooner than three months providing the attending physician is satisfied that his patient is clinically normal and able to carry out all safety measures under the conditions of his employment.

Some unmetabolized organic phosphorus insecticides are able to inhibit cholinesterase and are said to have a direct action; many other compounds are not active until they have been altered either by chemical or enzymatic change, and, therefore, are called indirect inhibitors. Direct inhibitors tend to have more prominent local effects and to produce systemic poisoning more rapidly.

Signs and Symptoms of Poisoning in Man: Signs and symptoms are, at least to a very great extent, secondary to cholinesterase inhibition. The usual symptoms include: headache, giddiness, nervousness, blurred vision, weakness, nausea, cramps, diarrhea, and discomfort in the chest. Signs include: sweating, miosis, tearing, salivation and other excessive respiratory tract secretion, vomiting, cyanosis, papilledema, uncontrollable muscle twitches, convulsions, coma, loss of reflexes, and loss of sphincter control. The last four signs are seen only in advanced cases **but do not preclude a favorable outcome if energetic treatment is continued.** Poisoned animals show various degrees of heart block, and cardiac arrest may occur. Following a massive oral dose associated with murder or suicide, death has occurred in 5 minutes or less after ingestion. Following smaller doses swallowed accidentally, onset of illness was sometimes delayed an hour or more. In occupational cases, illness is frequently delayed several hours so that the worker may first become sick at home after supper. (However, if symptoms begin more than 12 hours after the last known exposure to insecticide, illness is probably due to some other cause.) Furthermore, in occupational cases, relatively incapacitating symptoms of nausea, cramps, discomfort in the chest, muscular twitching, etc., often follow the initial giddiness, blurred vision, and headache only after a period of 2 to 8 hours, but the onset of serious symptoms may be more rapid. It seems that in the past undue emphasis has been given to miosis as a diagnostic sign. Miosis may appear late; in fact, the opposite condition, mydriasis, may be present, perhaps as a nonspecific reaction to the discomfort and apprehension associated with poisoning. Treatment of significant illness following excessive exposure to these compounds should not be delayed merely because miosis is absent.

There have been at least 3 cases in which artificial respiration was required but was inadequate, so that the patient survived temporarily but showed severe brain injury as a result of the anoxia. The reason for inadequacy of artificial respiration in different instances was delay in reaching the victim or resistance of the airway or other difficulty that could not be overcome by well-trained and well-equipped physicians. The patients gradually recovered from the specific signs of poisoning but remained comatose and tended to continue to have inadequate spontaneous respiration. Two of them showed temporary hyperthermia after the acute episode presumably as a result rather than a cause of brain injury. Death occurred 6 days to 4 weeks after onset. Extensive necrosis of the brain was present in those cases that came to autopsy.

Laboratory Findings: Leukocytosis and moderate albuminuria, acetonuria, and glycosuria are frequent and hemoconcentration may occur.

By special techniques, the cholinesterase level of the blood or serum may be shown to be greatly reduced. At autopsy, the same may be demonstrated for the cholinesterase level of the brain or other tissues provided fresh unfixed tissue is employed. Blood is usually adequate for examination if taken within a few days of death. Directions for collecting and shipping blood samples form Appendix C.

The most extensive single study of cholinesterase values of normal persons without exposure to organic phosphorus insecticides employed the Michel method (J. Lab. Clin. Med. **34**:1564; 1949) and revealed the following values:

Cholinesterase Activity (ΔpH/hr) of Normal Human Blood*

		Men	Women
Red cells	– range	0.39 – 1.02	0.34 – 1.10
	mean ± s.d.	0.766± 0.081	0.750± 0.082
Plasma	– range	0.44 – 1.63	0.24 – 1.54
	mean ± s.d.	0.953± 0.187	0.817± 0.187

*The means (but not the ranges) are for people 40 years old. On the average, the plasma cholinesterase of men increases about 0.02 per decade and that of women increases about 0.04 per decade. The enzyme activity of red cells does not change with age.

Other studies have shown that values exceeding the ranges in the table are encountered in normal people, but only very rarely.

It is believed that cholinesterase values of 0.5 or less for either cells or plasma represent abnormal depressions for most individuals. Nevertheless, people may experience far greater depressions (to 0.2 or less) without the onset of clinical signs or symptoms; this situation is especially true of workers who are exposed daily over a period of weeks but whose exposure at any one time is kept at a minimum. On the contrary, a considerable absorption of an organic phosphorus insecticide may occur in one or a few exposures without producing any measurable reduction of blood cholinesterase. For practical purposes, exposure to organic phosphorus or carbamate insecticides is the only cause of significant depression of cholinesterase activity. Certain diseases of the liver cause a reduction of the enzyme in the plasma, but these diseases are not consistent with active work.

It is also possible to estimate absorption of some of the organic phosphorus insecticides by analysis for their metabolic products in urine. Urinary levels of paranitrophenol have been used in this way to provide an estimate of parathion exposure. Other methods are available for other compounds. There is a broad correlation between the excretion of biotransformation products and the occurrence of illness. However, there are great individual differences in susceptibility.

Bradycardia, A-V block and dissociation, exaggeration and inversion of the T wave, and disappearance of the P wave have been observed in experimental animals poisoned by TEPP, and are likely to be encountered with other organic phosphorus insecticides under suitable conditions.

Pathology: No significant gross or microscopic pathology is to be expected except that associated with pulmonary or cerebral congestion or changes secondary to convulsions.

Differential Diagnosis: In the absence of laboratory facilities for cholinesterase determinations, brain hemorrhage, heat stroke, heat exhaustion, hypoglycemia, gastroenteritis, and pneumonia or other severe respiratory infection have been confused at times with poisoning by these compounds. Mild poisoning must frequently be distinguished from asthma and from simple fright with various psychosomatic manifestations, particularly among the associates of known poisoning cases. In recent years, a number of cases have been provisionally diagnosed as poisoning by one of the less toxic organic phosphorus insecticides before a complete investigation of the exposure history and clinical course changed the diagnosis to poisoning by more toxic insecticides, mercury fungicides, or solvents, or even to disease unrelated to pesticides.

Treatment:

I. In very severe cases, the order of treatment should be as follows:

(1) **ARTIFICIAL RESPIRATION,** if required, preferably by mechanical means. See Appendix E.

(2) **ATROPINE SULFATE,** 2 to 4 mg. (1/30 to 1/15 grain) intravenously as soon as cyanosis is overcome. Repeat at 5- to 10-minute intervals until signs of atropinization appear (drv, flushed skin and tachycardia as high as 140 per minute).

(3) **2-PAM, SLOWLY,** intravenously, 1 g. for adults and 0.25 g. for infants.

(4) **DECONTAMINATION** of the skin, stomach, and eyes as indicated.

(5) **SYMPTOMATIC TREATMENT.**

II. In the more usual case, proceed as follows:

(1) **ATROPINE SULFATE,** 1 to 2 mg. (1/60 to 1/30 grain), if symptoms appear. If excessive secretions occur, keep

the patient fully atropinized. Give atropine sulfate every hour up to 25 to 50 mg. in a day.

(2) **DECONTAMINATION** of the skin, stomach, and eyes as indicated.

(3) **2-PAM, SLOWLY,** intravenously, if the patient fails to respond satisfactorily to atropine sulfate. Dose of 1 g. for adults, 0.25 g. for infants.

(4) **SYMPTOMATIC TREATMENT.**

It will be noted that the recommended dosage of atropine sulfate is greater than that conventionally employed for other purposes but is within safe limits. Atropine sulfate relieves many of the distressing symptoms, reduces heart block, and dries secretions of the respiratory tract. People poisoned by anticholinesterase organic phosphorus compounds have an increased tolerance for atropine sulfate. Furthermore, a single dose of as much as 10 mg. of atropine sulfate has been inadvertently administered intravenously to normal adults without endangering life, although it has, of course, produced very marked signs of overdosage. In the presence of severe anticholinesterase poisoning, 40 mg. of atropine sulfate may be given in a day without producing symptoms attributable to atropine sulfate. The effects of intravenous atropine sulfate begin in 1 to 4 minutes and are maximal within 8 minutes. A mild degree of atropinization should be maintained in all cases for 24 hours, and in severe cases for at least 48 hours.

The tenacity of the chemical bond between cholinesterase and one of the various organic phosphorus compounds depends on the compound. For some, the bond is irreversible under ordinary conditimes. However, it has been found that certain derivatives of hydroxamic acid or oximes may promote release of the enzyme even when the bond is otherwise practically irreversible.

Three derivatives (one available in at least 3 forms) have proved outstanding:

(a) 2-Pyridine aldoxime methiodide (2-PAM iodide or pralidoxime iodide).

2-Pyridine aldoxime methochloride (2-PAM chloride or pralidoxime chloride)

2-Pyridine aldoxime methyl methanesulfonate (P2S)

(b) Diacetyl monoxime (DAM)

(c) 1,1′-Trimethylene-*bis*-(4-formyl pyridinium bromide) dioxime. (TMB-4).

One of these drugs, used in conjunction with atropine sulfate, will protect experimental animals from much larger doses of organic phosphorus compounds than is possible by the use of the drug or atropine sulfate alone. Of the three drugs, the first is best known. Tests carried out with 2-PAM on more than 40 people accidentally poisoned by parathion are most encouraging. The dosage used has usually been 1 g. for adults with proportionally smaller doses for infants. However, one patient severely poisoned by parathion received 40.5 g. of 2-PAM over a period of 6 days. In most cases, a single dose was sufficient to produce dramatic improvement within 30 minutes. In poisoning resulting from one or a few large doses of parathion, 2-PAM causes a marked reactivation of red cell cholinesterase but much less effect on the plasma enzyme. Side effects have been minimal in normal subjects and practically nonexistent in people who were poisoned. A few patients given the iodine preparation complained of a taste that no doubt resulted from the iodine moiety of the molecule. The other salts have the advantage of being more soluble and producing no taste. 2-PAM is rapidly excreted, chiefly in the urine. The half-life in the blood is about 1 hour.

2-PAM chloride is now available as an investigational drug under the Federal Food, Drug, and Cosmetic Act. The drug may be bought by qualified physicians from Campbell Pharmaceuticals, Inc. (121 East 24th Street, New York 10, N. Y.) after they file the necessary forms with the company. 2-PAM may also be obtained from and used under the supervision of the Public Health Service by qualified physicians who contact the medical officers listed on page 9.

Miosis and headache may persist after recovery from poisoning by organic phosphorus insecticides is otherwise largely complete. In some cases, the systemic administration of atropine sulfate is followed by partial or temporary dilatation of the pupils. Miosis responds more dependably to 2-PAM. If further systemic treatment is not necessary, the miosis and associated headache will respond to the instillation of 1/2% to 1% atropine sulfate solution or 1/2% atropine sulfate ointment into the eyes.

Never give morphine, theophylline, or theophylline-ethylenediamine (Aminophylline). Do not give atropine to a cyanotic patient; give artificial respiration first and then give atropine sulfate. Large amounts of intravenous fluids are generally contraindicated because of excessive fluid in the respiratory tract.

Tranquilizers should be used with great caution; they are seldom indicated at all. In fact, there are some indications that use of a phenothiazine-substituted drug to overcome anxiety and restlessness may have been a contributing cause in the fatal outcome of a case in which the side effects of the drug were apparently mistaken for persisting signs of poisoning by organic phosphorus insecticides. Promazine and chlorpromazine increase mortality in experimental animals poisoned by parathion.

If pulmonary secretions have accumulated before atropine sulfate has become effective, they should be removed by suction and a catheter. If the stomach is distended, empty it with a Levin tube.

If the patient has not yet shown symptoms or they have been allayed by treatment, he must be completely and quickly decontaminated. Remove the patient's clothing, and, with due regard for his condition at the moment, bathe him thoroughly. Remove any visible insecticide gently with lots of water and soap or other detergent, if available. Avoid abrasion. When the skin appears clear, bathe or swab with ethyl alcohol. Parathion and many of the other organic phosphorus insecticides are very much more soluble in alcohol than in water, and significant amounts can be washed from skin that has been scrubbed several times with soap and water.

If there is any suspicion that the poison has been ingested or inhaled and if the patient is still responsive, induce vomiting, give some neutral material such as milk or water, and induce vomiting again. The reason for mentioning inhaled material is, of course, that a large portion of such material may be deposited in the upper respiratory tract and subsequently carried to the pharynx and swallowed. Nausea may be anticipated, of course, on the basis of the systemic action of organic phosphorus compounds, but if vomiting is not profuse, gastric lavage may be used. Experiments have indicated that vomiting induced immediately or even 1.5 hours after ingestion is more effective than gastric lavage in removing poison.

Atropine sulfate does not protect against muscular weakness. The usual mechanism of death appears to be respiratory failure. The use of an oxygen tent or even the use of oxygen under slight positive pressure is advisable and should be started early. **Watch the patient constantly, since the need for artificial respiration may appear suddenly.** Equipment for oxygen therapy and for artificial respiration should be placed by the patient's bed in readiness while the patient is on his way to the hospital. Cyanosis should be prevented by the most suitable means, since continued anoxia aggravates the depression of the respiratory center caused directly by the poison. Complete recovery may occur even after many hours of artificial respiration have been necessary.

If there is any reason to think that the eyes may have been contaminated, irrigate them with physiological saline or water. The absorption of some of the organic phosphorus insecticides by the eye is remarkably rapid.

The acute emergency lasts 24 to 48 hours, and the patient must be **watched continuously** during that time. Favorable response to one or more doses of atropine sulfate, frequently given as a first aid measure, does not guarantee against sudden and fatal relapse. Medication must be continued during the entire emergency.

Any person who is ill enough to receive a single dose of atropine sulfate should remain under medical observation for 24 hours, because the atropine sulfate may produce only a temporary relief of symptoms in what may prove to be a serious case of poisoning. Atropine sulfate should never be administered for preventive purposes to persons who have not become sick. 2-PAM is not used as first aid, and one dose of it is frequently adequate. However, repeated administration may be required in severe cases, and the patient always must have continuous observation.

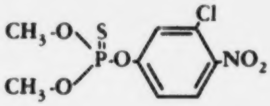
Following exposure heavy enough to produce symptoms, further organic phosphorus insecticide exposure of any sort should be avoided. The patient may remain susceptible to relatively small exposures to the same or any other organic phosphorus compound until regeneration of cholinesterase is nearly complete.

Prevention: Poisoning in those who work with the more toxic organic phosphorus insecticides may be prevented in three general ways: (1) constant, thoughtful care on the part of every worker; (2) mechanical aids such as protective clothing, masks, and factory safety ventilation; and (3) regular inspection of working conditions. It is practical to test routinely the plasma and erythrocyte cholinesterase levels of factory or agricultural workers who may be subject to significant exposure to organic phosphorus compounds. The interpretation of individual values in asymptomatic persons is difficult. It is clear, however, that a single very low enzyme value for one worker or a low average value for a group of exposed workers is an indication of the need for improved personal care or better mechanical protection or both. In a similar way, poisoning may be minimized by proper evaluation of the amount of urinary excretion of biotransformation products, such as paranitrophenol.

Chlorthion

Chemical Name: 0,0-dimethyl 0-(*m*-chloro-*p*-nitrophenyl) phosphorothioate:

Chemical Formula:



Formulations: Chlorthion is available as an approximately 50% emulsifiable concentrate, 25% water-wettable powder, and 3% dust.

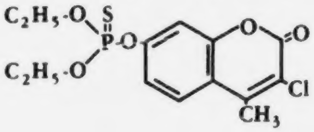
Uses: Chlorthion is used in control of roaches and adult and larval mosquitoes. It is approved for use in dairy barns for fly control.

Toxicology: No cases of human poisoning are known. Studies of the acute oral and dermal toxicity of Chlorthion to experimental animals indicate a low toxic hazard. By both oral and dermal routes, the toxicity of Chlorthion is less than that of DDT and much less than that of certain other of the organic phosphorus group of insecticides. From animal studies, one might expect some cholinesterase depletion in persons having very heavy repeated exposures to Chlorthion. Taking dosage into account, the toxicology of Chlorthion is similar to that of the organic phosphorus insecticides generally. See pages 12 to 23.

Co-Ral

Chemical Name: 0,0-diethyl 0-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl)phosphorothioate.

Chemical Formula:



Formulations: Co-Ral is available in the form of a 25% wettable powder and 0.5% dust.

Uses: Co-Ral is a systemic insecticide for control of arthropod parasites of animals by external application. Sprays and dips of 0.25% and 0.5% concentration are used to control cattle grubs as well as external parasites of cattle, sheep, goats, dogs, and chickens.

Routes of Absorption: Co-Ral can be absorbed through the skin as well as by other routes.

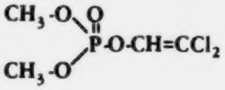
Pharmacologic Action: See page 12. Co-Ral differs from many other organic phosphates in that the toxicity as a result of oral administration is delayed and more prolonged.

Toxicology: The dermal toxicity of Co-Ral is low. No toxic symptoms due to the use of Co-Ral have been observed in man. However, excessive exposure has been shown in a few cases to lower blood cholinesterase values. The ingestion of significant quantities would be expected to produce poisoning. Taking dosage into account, and with the possible exception of its delayed action, the toxicology of Co-Ral is similar to that of the organic phosphorus insecticides generally. See pages 12 to 23.

DDVP

Chemical Name: O,O-dimethyl 2,2-dichlorovinyl phosphate.

Chemical Formula:



$$\begin{array}{l} CH_3\text{-}O\diagdown\overset{O}{\|} \\ \qquad\quad P\text{-}O\text{-}CH{=}CCl_2 \\ CH_3\text{-}O\diagup \end{array}$$

Formulations: Technical, baits, concentrates, and aerosols are available.

Uses: DDVP is used for control of houseflies, phorid flies (in mushroom cultures), Mediterranean fruit flies, and cigarette beetles (in warehouses).

Routes of Absorption: DDVP is easily absorbed by the skin as well as by other routes. Although inherently less poisonous than parathion or TEPP, it has a much greater vapor pressure, and toxic concentrations of DDVP may be produced in special chambers in the laboratory. Measurements show that dangerous concentrations of vapor are not produced under practical conditions of use in warehouses, but fogs or aerosols may be dangerous.

Phamocologic Action: In general, the action is similar to that of other organic phosphorus insecticides, but the compound is a direct inhibitor of cholinesterase, and it is detoxicated relatively quickly. At least in animals, recovery from acute poisoning is rapid and the range of tolerated dosage is wide. Although a dietary concentration of DDVP as low as 50 ppm produces definite lowering of the plasma and red cell cholinesterase levels of rats, yet these animals withstand a dietary level of 1,000 ppm for 90 days without showing any signs of intoxication.

Dangerous Single and Repeated Doses to Man: Two laborers in another country died after spilling concentrated DDVP on their arms. No details are available.

In another instance, the spillage of only about 4 ounces of a 3% oil solution of DDVP on a man's lap resulted in poisoning which apparently would have been fatal had it not been for unusually vigorous treatment. There was no previous exposure and no effort to remove the poison until the man noticed a burning of the skin about half an hour after the accident. Even then, washing was very superficial and a bath was delayed another hour.

In still another case, a man spilled a smaller amount of the same 3% formulation on his arm. He removed his shirt at once and washed with soap and water as soon as possible, about 15 minutes later. He developed dizziness and nausea as the only symptoms.

Tests have shown that men can withstand brief exposure to air concentrations at least as high as 6.9 μg./1. without clinical effect or depression of blood cholinesterase; intermittent exposure totaling 5 hours daily at a concentration of 0.5 μg./1. produces no clinical effect and no effect on red cell cholinesterase, but does cause a gradual, moderate reduction of plasma cholinesterase.

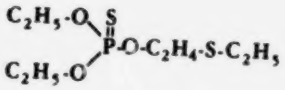
Signs and Symptoms of Poisoning in Man: In the serious, nonfatal case mentioned above, the victim developed slurred speech and drowsiness slightly more than an hour and a half after the accident. He collapsed suddenly after reaching a hospital. Prompt use of oxygen, a total of 15 mg. of atropine sulfate (mostly intravenously), and supportive treatment saved him. He appeared to be recovering uneventfully when he developed periodic hallucinations and violent combativeness during the fourth and fifth day after the accident. Because of certain factors peculiar to this case, it was not possible to tell whether these complications were related directly to DDVP. In any event, the patient finally recovered completely.

Laboratory Findings and Other Toxicology: See page 16. The first sample of blood for cholinesterase determination in the serious, nonfatal case mentioned above was taken the day after the accident. The enzyme activity, though reduced, was surprisingly high in view of the near-fatal outcome. Animals show a rapid recovery of cholinesterase activity, especially of the plasma, following poisoning with DDVP. The same may occur in man. For other points of toxicology, see pages 12 to 23.

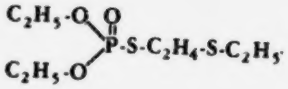
Demeton

Chemical Name: O,O-diethyl O-[2-(ethylthio)ethyl]phosphorothioate (I) and O,O-diethyl S-[2-(ethylthio)ethyl]phosphorothioate(II) in a ratio of approximately 2 to 1.

Chemical Formulae:



I. Thiono Isomer



II. Thiol Isomer

Formulations: Demeton is available as an approximately 24% emulsifiable concentrate.

Uses: Demeton is a systemic insecticide in plants; that is, the compound is translocatable from one part of a living plant to another. Thus, demeton will control certain plant pests on all parts of the plant, even though it may be applied to only one part. The compound is used on cotton, ornamentals, seed crops, and some food plants.

Routes of Absorption: Demeton is readily absorbed through the skin, as well as by other portals.

Pharmacologic Action: See page 12.

Dangerous Single and Repeated Doses to Man: Little is known regarding the acute and repeated dosages that would be dangerous to man. However, the minimum acute lethal oral dose for man is believed to be approximately equal to that of parathion. The compound is only slightly less toxic by the dermal route. In the female rat, a dietary intake at the rate of 0.16 mg./kg./day produced slight cholinesterase depression. An intake of 2.6 mg./kg./day caused signs of poisoning that tended to diminish as feeding continued. Men tolerated 3.75 mg. daily for 24 days (approximately 0.05 mg./kg./day) with only about 15% depression of plasma cholinesterase and no significant change of red cell enzyme.

Signs and Symptoms of Poisoning in Man: At least four fatal, several severe nonfatal, and a number of mild cases of demeton poisoning have been reported. Persons poisoned with demeton have shown the typical symptoms of organic phosphorus poisoning described on page 15.

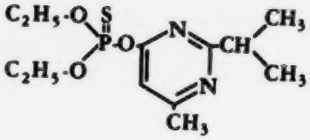
Pathology: One autopsy revealed congestion in the viscera, a bloody exudate in the lungs, and a unique odor of the contents of the peritoneal cavity.

Treatment and Other Toxicology: See pages 12 to 23.

Diazinon

Chemical Name: O,O-diethyl O-(2-isopropyl-4-methyl-6-pyrimidinyl) phosphorothioate.

Chemical Formula:



Formulations: Diazinon is available in the technical form (about 90% pure), as a 25% wettable powder, 2% to 4% dust, 25% emulsifiable concentrate, 20% solution, and as a poison bait. For fly control, the addition of sugar (2.5 parts sugar to 1 part of toxicant) has been used.

Uses: Diazinon is effective against flies and roaches as well as many insect pests of fruits and vegetables. In addition to the more usual formulations, it may be used to impregnate cords for fly control.

Routes of Absorption: Diazinon is readily absorbed through the skin as well as through other portals.

Dangerous Single and Repeated Doses to Man: Eight men drank only part of a bottle of Diazinon dissolved in xylene or a xylene-like material in the belief that the liquid was wine. Three of them, with an average age of 73 years, died.

Diazinon, formulated as an ointment, caused sweating, abdominal pain, nausea, and, in one instance, coma when 80 mg. of active ingredient was applied experimentally twice to the skin of each of two men for the treatment of creeping eruption. It is not possible at this time to state whether the unexpectedly great dermal absorption was caused by the formulation or the dermatitis, or both.

The spraying of an oil formulation on floors and bedclothing caused near-fatal poisoning of 3 children.

Slight asymptomatic cholinesterase depletion occurs in spraymen as a result of extensive occupational exposure to Diazinon. This fact and the cases mentioned show that Diazinon must be used with care even though its toxicity is relatively low in comparison with many other organic phosphorus insecticides.

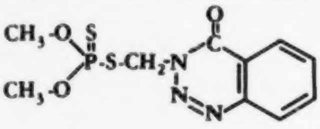
Signs and Symptoms of Poisoning in Man: Typical symptoms (listed on page 15) occurred in the cases of Diazinon poisoning. Miosis, bradycardia, diarrhea, increased respiratory tract secretions, coma, and convulsions were seen in one or more cases, including those that survived. The illness tends to be somewhat more protracted than poisoning by most other organic phosphorus compounds.

Laboratory Findings and Other Toxicology: Serious illness is associated with very marked inhibition of blood cholinesterase. For treatment and other aspects of toxicology, see pages 18 to 23.

Guthion

Chemical Name: O,O-dimethyl S-(4-oxo-1,2,3-benzotriazin-3 (4H)-ylmethyl)phosphorodithioate.

Chemical Formula:



Formulations: Guthion is available as an approximately 18% emulsifiable concentrate, as 25% wettable powder, and as 3% dust.

Uses: Guthion is currently used in controlling a wide variety of insects on fruit, nuts, cotton, and some vegetables.

Routes of Absorption: Guthion can be absorbed through any body portal.

Dangerous Acute and Repeated Doses to Man: There is little direct knowledge of the acute and chronic dosages that would be dangerous to man. Although the acute oral toxicity is similar to that of parathion, the dermal toxicity is considerably lower than that of most other highly toxic organophosphorus pesticides. This difference may account for the better safety record of Guthion. Dogs that were fed diets containing 20 ppm of Guthion for 12 weeks exhibited no toxic symptoms, although their red blood cell cholinesterase was depressed to about 80% of normal.

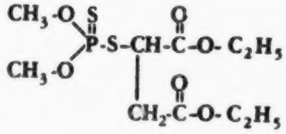
Signs and Symptoms of Poisoning in Man: No fatal cases of poisoning with Guthion are known. People with occupational exposure have an excellent safety record similar to that of people using malathion.

Other Toxicology: The toxicology of Guthion is similar to that of the organic phosphorus compounds generally. See pages 12 to 23.

Malathion

Chemical Name: O,O-dimethyl S-(1,2-dicarbethoxyethyl) phosphorodithioate.

Chemical Formula:



$$\begin{array}{l} CH_3\text{-}O \\ CH_3\text{-}O \end{array}\!\!>\overset{S}{\overset{\|}{P}}\text{-}S\text{-}\begin{array}{l} CH\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}C_2H_5 \\ | \\ CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}C_2H_5 \end{array}$$

Formulations: Malathion is available as technical grade material, wettable powder (25%), dusts, solutions, poison baits, and emulsifiable concentrates.

Uses: Malathion is used in the control of certain pests of fruits, vegetables, and ornamentals. As a public health pesticide, it has been employed for the control of house flies, mosquitoes, and lice. For fly control, malathion is used in liquid and dry baits.

Routes of Absorption: Malathion is absorbed by all portals, but skin absorption is inefficient (see below).

Pharmacologic Action: Much of the malathion taken into the mammalian body is broken down, chiefly in the liver, into harmless materials, but some is converted into compounds that inhibit cholinesterase and, therefore, may produce the characteristic signs and symptoms caused by other organic phosphorus compounds (see page 15). Massive doses of malathion produce temporary muscular weakness in chickens, which, like man, are susceptible to this kind of effect. Affected chickens continue to show this paresis for up to three weeks after full recovery from the ordinary signs of malathion poisoning. Moderate doses produce no such effect, and the compound is practical for the control of ectoparasites of chickens. The mechanism by which the muscular weakness is produced is not known, but it is clearly not identical to that responsible for other poisoning. The muscular weakness, such as that seen in chickens, has not been seen in human cases (perhaps because of dosage); its relationship to the coma and flaccidity seen in some human cases is not known.

Dangerous Single and Repeated Doses to Man: A dose of only about 4 g. of malathion produced severe but nonfatal illness in a child who drank it, and a dose of 14 g. had a similar effect on a woman. On the contrary, an amount estimated at 5 g. led to the death of a 75-year-old man about 1.5 hours after ingestion. A second fatality resulted from an estimated 56.7 g. of malathion. All confirmed cases, whether fatal or not, have involved proved or possible ingestion as determined by history or the finding of malathion in stomach washings, or both. Five cases reported as malathion poisoning presumably involved dermal or respiratory exposure. These cases show little clinical resemblance to confirmed cases or to one another. An oral dose of 58 mg. taken experimentally produced no clinical effect and 23% of the dose was recovered in the urine. A total of 1106 mg. was recovered from the urine of a man who barely recovered following attempted suicide.

The repeated dosage of malathion necessary to produce clinical illness in man is unknown. Experiments have shown that people can eat 16 mg. of malathion daily without significant depression of cholinesterase or any clinical effect. A dosage of 24 mg. per day for 56 days produced a maximal reduction of 25% in both plasma and red blood cell cholinesterase. Ten percent malathion powder was applied daily to essentially all the human skin, and an average of 2% of the available dose was recovered in the urine. When this dosage was repeated daily, an average daily excretion of 51.5 mg. of malathion-equivalent was recovered. The maximal rate of excretion measured in this way with no clinical side effects was 229 mg. per day. The rate of malathion absorption was undoubtedly somewhat greater than the rate of recovery of malathion-equivalent in the urine. Very extensive use of malathion has not led to depletion of blood cholinesterase in applicators. The threshold limit value for malathion in air is 15 mg./M^3.

Signs and Symptoms of Poisoning in Man: Broadly speaking, the signs and symptoms observed in poisoning by other organic phosphorus compounds have been seen in poisoning by malathion. However, sudden coma (characterized by unconsciousness and marked flaccidity of the limbs, but without cardiovascular collapse and with minimal interference with respiration) occurred in several cases that went on to uneventful recovery. (A similar flaccidity with minimal interference with respiration has been reported more rarely in people poisoned by parathion.) In at least one case of malathion poisoning, coma was recurrent. Involuntary defecation and urination occurred during coma in several instances. Some patients seemed to respond promptly to atropine sulfate, while others showed less response than might be expected. Cholinesterase was only moderately depressed when illness was severe, but was severely depressed in a fatal case in which the measurement was made. Thus, there is more than a hint that poisoning by malathion is characterized in man by "side effects" not seen in poisoning by inherently more toxic organic phosphorus compounds. In any event, it is clear that a relatively large dose of malathion is required to produce illness and that the chances of recovery from this illness are better than might be judged from the clinical appearance of the patient.

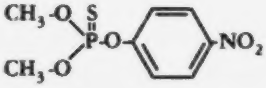
Laboratory Findings: In the few cases in which blood cholinesterase was measured, the red cell and plasma enzymes were about 40% to 50% of normal, which was higher than the clinical severity of the cases would have led one to predict.

Treatment and Other Toxicology: See pages 18 to 23.

Methyl parathion

Chemical Name: O,O-dimethyl O-(*p*-nitrophenyl) phosphorothioate.

Chemical Formula:



Formulations: Methyl parathion is available as 70% solution, 24% to 51% emulsifiable concentrates, and 25% dust concentrate. It is applied in the form of dilute sprays or dusts (1.5% to 5%).

Uses: Control of agricultural pests.

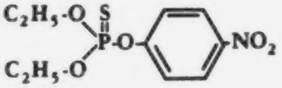
Routes of Absorption: Methyl parathion may be absorbed by any route.

Toxicology: The dangerous dose is not known. An oral dosage of 7.0 mg. daily for 24 days (approximately 0.1 mg./kg./day) produced no significant effect on red cell cholinesterase and only about 15% inhibition of the plasma enzyme of volunteers. All confirmed cases of human poisoning have had substantial exposure. In what may have been the only fatal case, the compound was recovered from the stomach and must have been ingested. Animal experiments indicate a somewhat lower dermal toxicity than that for parathion. This finding may be a factor in explaining the relatively good occupational safety record of methyl parathion. For treatment and other aspects of toxicology, see pages 18 to 23.

Parathion

Chemical Name: O,O-diethyl O-(*p*-nitrophenyl) phosphorothioate.

Chemical Formula:



Formulations: Parathion is currently used as dilute sprays, which are prepared by the operator from 15% or 25% wettable powders or from emulsifiable concentrates of 50% or less. Dusts are used also. They may be purchased ready mixed in concentrations of 5% or less. Technical parathion, which is a deep brown to yellow liquid and approximately 98% pure, may be encountered under industrial conditions and in formulating establishments. Aerosol formulations containing up to 10% parathion may be used in greenhouses. Cords impregnated with parathion for fly control contain about 100 mg. per linear foot.

Uses: Parathion finds almost its entire use in agriculture including nurseries, greenhouses, etc. Persons exposed occupationally to parathion may be engaged in synthesizing the compound, formulating and packaging it, applying it, or working among residues. Even those workers whose only contact has been with fresh residues have occasionally been poisoned. This has been noted among such crop workers as thinners, harvesters, and irrigators. Accidental exposure of children to open or even "empty" containers has been a major and dramatic source of fatal poisonings.

Under practical field conditions, agricultural workers may have approximately concurrent exposure to two or more organic phosphorus pesticides. The patient may recall only the most recent use of the most advertised formulation; a careful history is necessary to reveal the facts.

Routes of Absorption: Absorption takes place readily through any portal. Fatal human poisoning has followed ingestion, skin exposure, and also inhalation with varying degrees of skin exposure. The vapor pressure of parathion is so low that respiratory exposure alone is not considered important as a cause of serious poisoning from wet sprays. Respiratory exposure to finely particulate dust is hazardous; complete respiratory protection has reduced illness among formulating plant workers. Aerosol preparations are known to be highly dangerous.

Pharmacologic Action: See page 12.

Dangerous Single and Repeated Doses to Man: Death has followed splashing of the body and clothing of one worker with technical parathion (approximately 95% pure). The amount was sufficiently small that the worker was not soaked or at any rate did not follow the simple instructions for changing clothes and bathing. Several operators have died after rather extensive skin contact with dilute agricultural sprays or dusts. Children 7 to 9 years old were killed by bathing in a tub in a house that had been sprayed several days earlier with 10% parathion intended for ornamental plants in a greenhouse. Other children died after swinging on a parathion contaminated bag suspended by a rope. Both children and adults have been poisoned by parathion applied with the intention of controlling head lice or other lice.

In a number of fatal cases of human poisoning by parathion, the dosage which the victim received orally was known to be exactly 900 mg. In one carefully studied case, the ingestion of 120 mg. led rapidly to death of a man. Children 5 to 6 years old were killed by eating 2 mg. of parathion, a dosage of about 0.1 mg./kg. In instances in which parathion contaminated food eaten by people of different ages, death occurred mainly or exclusively among children.

A daily oral dose of 7.2 mg. produced a 33% fall in whole blood cholinesterase of adult volunteers in 42 days. A dose of 3 mg./day produced no effect. The established threshold limit for parathion in air is 0.1 mg./M^3.

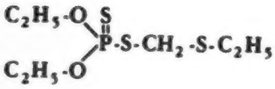
Laboratory Findings: See page 16. Under certain circumstances, parathion may be isolated from exhumed bodies as well as fresh necropsy specimens.

Treatment and Other Toxicology: See pages 18 to 23.

Phorate

Chemical Name: O,O-diethyl S-(methylthio-ethyl)phosphorodithioate.

Chemical Formula:



$$\genfrac{}{}{0pt}{}{C_2H_5\text{-}O}{C_2H_5\text{-}O}{>}\overset{S}{\overset{\|}{P}}\text{-}S\text{-}CH_2\text{-}S\text{-}C_2H_5$$

Formulations: Carbon impregnated with 44% phorate.

Uses: Seed treatment of cotton and legumes.

Dangerous Single and Repeated Doses to Man: The dangerous dose of phorate for man is unknown but obviously small.

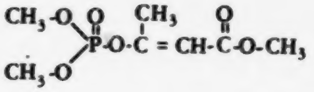
Signs and Symptoms of Poisoning in Man: The signs and symptoms described on page 15 have occurred in cases associated with phorate. One patient suffered occasional convulsions and a severe fall in blood pressure. He required artificial respiration but ultimately recovered.

Treatment and Other Toxicology: See pages 18 to 23.

Phosdrin

Chemical Name: alpha isomer of 2-carbomethoxy-1-methylvinyl dimethyl phosphate.

Chemical Formula:



$$(CH_3\text{-}O)_2\overset{O}{\overset{\|}{P}}\text{-}O\text{-}\overset{CH_3}{\overset{|}{C}}=CH\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}CH_3$$

Formulations: Technical Phosdrin contains not less than 60% of the alpha isomer listed above, the remainder being insecticidally active related compounds. It is available as approximately 25% and 50% concentrates, 25% water-soluble solutions, 1% and 2% dusts, 1% and 2% granules, and 20% to 25% wettable powders.

Pharmacologic Action: Phosdrin is a direct inhibitor of cholinesterase. It, therefore, shares with TEPP the unusual property of causing miosis in the presence of mild or even no systemic illness. It is also distinguished by its ability to cause other local effects and by its high toxicity and rapid onset of systemic symptoms.

Dangerous Acute and Repeated Doses to Man: The dangerous dose of Phosdrin for man is unknown. However, animal experiments and human cases show that it is very small. The tentative threshold limit value for Phosdrin in air is 0.1 mg./M^3.

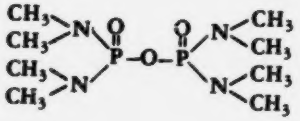
Signs and Symptoms of Poisoning in Man: Most observed cases have been occupational in origin. In general, the signs and symptoms described on page 15 have been seen, but presence of visual disturbance and rapidity of onset have been noteworthy and are probably associated with direct inhibition of cholinesterase. Illness has begun within 15 minutes of spillage of the insecticide and within 45 minutes of first exposure.

Treatment and Other Toxicology: See pages 18 to 23.

Schradan

Chemical Name: octamethylpyrophosphoramide

Chemical Formula:



Fomulations: Sprays and aerosol bombs (7%). Concentrations as high as 42% are available.

Uses: Schradan is a systemic insecticide absorbed by plants and translocated to all parts for the control of sucking insects.

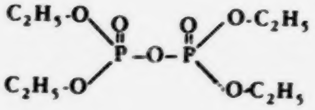
Dangerous Single and Repeated Doses to Man: Apparently, human illness as the result of exposure to schradan has not been reported. The ingestion of 1 mg. of schradan per day caused a gradual, asymptomatic depression of blood cholinesterase (especially red cell enzyme) in 24 volunteers. The depression was maximal (25% in whole blood) after about 40 days. The ingestion of 4.2 mg. of schradan per day by one subject caused a maximal depression of whole blood cholinesterase (67%) after about 60 days of the 74-day exposure period. Patients with myasthenia gravis have been maintained on doses of 7 mg. every 12 hours for months with apparent benefit and on doses of 15 mg. every 12 hours with some signs of intoxication.

Treatment and Other Toxicology: See pages 18 to 23.

TEPP

Chemical Name: tetraethyl pyrophosphate.

Chemical Formula:



Formulations: Formulations (all expressed as technical TEPP*) include concentrates (solutions of the organophosphates and emulsifiers in an organic solvent) ranging up to 50% or more and field-use emulsions ranging from 0.025% to 0.4%, aerosols from 0.5% to 4%, and dusts from 0.5% to 2.0%. A mixture of 4.7% TEPP and 10.7% lindane has been used for fly control after dilution with a solution of molasses which serves as a bait.

Uses: TEPP is used as a substitute for nicotine in the control of aphids, mites, and other soft-bodied arthropods. Its use in the control of insects of public health importance has been limited almost entirely to fly control.

Routes of Absorption: TEPP is absorbed readily through all portals. In the rat the relation between the LD_{50} by subcutaneous, oral, and percutaneous administration is 1 : 2.5 : 3.5.

Dangerous Single and Repeated Doses to Man: Fatal accidents involving TEPP have apparently all involved suicide or gross carelessness, such as taking the compound by mouth or spilling a concentrate of it on the skin. The dosages in such cases are, of course, unknown. Several persons, including children, have died after spilling the concentrated material on their skin. A number of nonfatal accidents have been reported among agricultural workers and airplane pilots who were making agricultural application of the insecticide. Some experience has been had in man in connection with the treatment of myasthenia gravis. A single dose of 5 mg., or 3.6 mg. daily for 2 days, or 2.4 mg. daily for 3 days parenterally; or 7.2 mg. every 3 hours orally for 3 to 5 doses, produced symptoms in normal subjects as did slightly larger doses in myasthenia gravis patients receiving atropine sulfate. Symptoms at these relatively low dosages included localized fasciculations, anorexia, nausea, sweating, abdominal cramps, salivation, giddiness, restlessness, insomnia, paresthesias, and dreaming. Symptoms appeared suddenly about 30 minutes after the final dose.

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*The technical grade material is 40% TEPP and 60% related ethyl phosphates, which are also active.

Evidence has been obtained that 5 mg. intramuscularly or 25 mg. orally would cause severe symptoms. Likewise, it is believed that 20 mg. intramuscularly or 100 mg. orally would cause death. It will be noted that the single oral dose of 25 mg. per man mentioned above represents a dosage of only about 0.35 mg./kg.

The threshold limit value for TEPP in air is 0.05 mg./M^3.

Signs and Symptoms of Poisoning in Man: In addition to the systemic poisoning effects listed on page 15, the following local effects should be mentioned. Since TEPP is a direct inhibitor of cholinesterase, it may produce ophthalmic and possibly pulmonary signs and symptoms without accompanying systemic illness. The picture produced by ophthalmic instillation of 0.1% technical TEPP in peanut oil consisted of excess lacrimation, rhinitis, burning, mild blurring of vision, mild headaches, sensations of pressure in the eyeballs or over the frons and, within 20-30 minutes, pin-point pupils with accompanying increased accommodation and diminished light perception. Most of these signs and symptoms disappeared in a few hours, but considerable miosis persisted for 24 hours and the effects were not all gone after 48 hours. When instillation was limited to one eye, resulting in unilateral miosis, the volunteers complained of disturbance of depth perception even though they passed standard tests of static depth perception. This complaint was due to the production of the Pulfrich phenomenon brought on by the unequal light in the two eyes. Similar effects, especially miosis, have occurred in agricultural workers, including pilots, who were exposed in the course of their work.

There is evidence, especially with dusts, that there may be signs of TEPP poisoning restricted to the respiratory system. Rhinitis and a sensation of tightness in the chest may be due entirely to the localized effect of the TEPP. Local effects from parathion or demeton are less apparent.

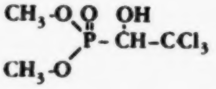
Laboratory Findings: See page 16.

Treatment and Other Toxicology: See pages 18 to 23.

Trichlorofon

Chemical Name: O,O-dimethyl,2,2,2-trichloro-1-hydroxyethyl phosphonate.

Chemical Formula:



$$(CH_3O)_2\overset{O}{\overset{\|}{P}}-\overset{OH}{\overset{|}{CH}}-CCl_3$$

Formulations: Trichlorofon is available as a 1% dry bait for fly control. Other formulations are 50% wettable powder, 5% dusts and granules, and fly disks each of which contains 0.1 g.

Uses: This material is used in dairy barns and milk processing rooms as a poison bait for fly control. It is also used for control of roaches and a variety of insect pests of field crops and ornamentals. More recently the compound has been used, either as an oral dose or spray for control of cattle grubs, horse bots, screw worms, various arthropod ectoparasites, and several nematode worms.

Routes of Absorption: Trichlorofon is readily absorbed through the skin as well as by other routes.

Pharmacologic Action: See page 12. Trichlorofon is a weak direct inhibitor of cholinesterase. It differs from other compounds in this group with respect to the very rapid recovery from symptoms of sublethal poisoning noted in experimental animals.

Dangerous Single and Repeated Doses to Man: A highly purified trichlorofon formulation given in two doses of 7.5 mg./kg. on succeeding days to 15 volunteers (a total dose of 1,050 mg. for a 70 kg. man) produced nausea, colic, and sweating in one and no illness in the others. The affected person recovered after a single dose of atropine sulfate. The plasma cholinesterase level fell to below 10% of normal, and the red cell cholinesterase fell to about 50% in all the subjects. Later, this same dosage was used extensively for the treatment of intestinal worms with infrequent and mild side effects.

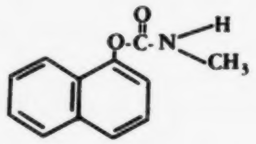
Other Toxicology: Taking into account the high dosage of trichlorofon necessary to produce poisoning in man or animals, and also taking into account the rapidity of recovery, the toxicology of trichlorofon is otherwise similar to that of the organic phosphorus insecticides generally. For treatment and other aspects of toxicology, see pages 18 to 23.

CARBAMATE INSECTICIDES

Carbaryl

Chemical Name: 1-naphthyl-N-methylcarbamate

Chemical Formula:



Formulations: Carbaryl is manufactured as a 98% concentrate which is formulated for use as dusts (1.75% to 10%), wettable powders (50% to 80%), and flowable formulations (40% to 50%).

Uses: Carbaryl is a wide spectrum insecticide effective against insect pests of fruits and nuts, vegetables, forage crops and cotton, and forest and range land.

Routes of Absorption: Carbaryl is absorbed by all portals including the skin.

Pharmacologic Action: The carbamates are reversible inhibitors of cholinesterase. The reversal is so rapid that, unless special precautions are taken, measurements of blood cholinesterase of people or animals exposed to carbamates are likely to be inaccurate and always in the direction of appearing to be normal. The compound is rapidly metabolized. The naphthalene moiety is excreted as 1-naphthol, largely in a conjugated form. Concentrates may cause skin irritation as well as systemic poisoning.

Dangerous Acute and Repeated Doses to Man: A single, carefully-measured oral dose of 250 mg. (approximately 2.8 mg./kg.) resulted in moderately severe poisoning of an adult. The smallest dosage that will produce illness in man following prolonged exposure is not known. Because of the rapid metabolism, the dangerous repeated dose may be only slightly smaller than the dangerous single dose. Workers exposed to carbaryl dust, sometimes at concentrations as high as 40 mg./M^3 under abnormal conditions but usually at lower concentrations, showed a slight depression of blood cholinesterase but no illness. Dogs were acutely poisoned when exposed in a chamber at a concentration of 75 mg./M^3 for 5 hours.

In the male rat, the oral LD_{50} is 850 mg./kg. and the dermal LD_{50} is >4,000 mg./kg. Carbaryl was fed to male and female rats for 92 days at levels as high as 225 to 237 mg./kg./day without significant effect on food consumption, rate of growth, or level of plasma or red cell cholinesterase. Single oral doses at the highest level depressed the plasma and red cell cholinesterases but the activities of these enzymes came back to normal within 16 hours.

Signs and Symptoms of Poisoning in Man: A 19-month old infant developed constriction of the pupils, salivation, and muscular incoordination in spite of gastric lavage within half an hour after ingestion of an unknown amount of carbaryl. A single 0.3 mg. dose of atropine sulfate was effective, and recovery was apparently complete in 12 hours. The man who swallowed 250 mg. of carbaryl had a very sudden onset of violent epigastric pain 20 minutes after the dose. A little later he began to sweat profusely. A 1 mg. dose of atropine sulfate produced little improvement although he was still able to continue work. He gradually developed great lassitude and vomited twice. One hour after ingesting carbaryl, and following a total of 3 mg. of atropine sulfate, he was feeling better. After one more hour he was completely recovered and enjoyed lunch.

Laboratory Findings: Blood cholinesterase is inhibited; it should be measured by a technique that minimizes reactivation. 1-Naphthol, a compound normally present only in traces, is excreted in the urine following absorption of carbaryl. A specimen collected 18 hours after poisoning from the infant mentioned above contained a concentration of 31.4 ppm. Healthy men with occupational exposure have been found to excrete conjugated plus free 1-naphthol at a rate of 10 ppm or slightly higher, while unexposed men excrete 1.5 to 4.0 ppm.

Treatment: Depending on the severity of the case, all the methods used for treating poisoning by organic phosphorus compounds are useful with one exception: **2-PAM and other oximes are not recommended for routine use.** Animal studies indicate that the use of 2-PAM might be harmful. Although people might not show the same reaction, no oxime should be used for treating poisoning by a carbamate insecticide except on an investigational basis.

CHLORINATED HYDROCARBON INSECTICIDES

Introduction: The chlorinated hydrocarbon insecticides have in common the chemical composition implied in the group name. However, beyond this broad similarity, the compounds vary widely in chemical structure and activity. Although much is known about the pharmacology of these materials, the basic mode of action is not known for a single one of them. It is entirely possible that chlorinated hydrocarbon insecticides of significantly different chemical structure have different modes of action; it is certain that there are qualitative as well as quantitative differences in their pharmacologic action.

The acute oral and dermal LD_{50}-values to rats of certain chlorinated hydrocarbon insecticides and derivatives including those treated in this Handbook are given in the table (page 48).

The following description, based largely on DDT, is applicable to the chlorinated hydrocarbon insecticides as a group. The actions known to be peculiar to specific compounds are described in the separate sections.

Pharmacologic Action: The chlorinated hydrocarbon insecticides act on the central nervous system, but the exact mechanism of this action either in man or in animals has not been elucidated. Large doses also induce nausea and/or diarrhea. On repeated dosage, the compounds produce microscopic changes in the liver and kidneys in some experimental animals. This has not been demonstrated clearly in man in connection with uncomplicated poisoning. Somewhat different lesions may be produced in man or animals by a single fatal dose.

The compounds and/or certain degradation products are stored in fat. Such storage results either from a single large dose or from repeated small doses. The materials stored in the fat appear to be largely inactive, since the total amount stored in an experimental animal often may be greater than the lethal dose if given at one time. The insecticides (or their derivatives) usually may be demon-

ACUTE ORAL AND DERMAL LD_{50}-VALUES OF CHLORINATED HYDROCARBON INSECTICIDES FOR MALE AND FEMALE WHITE RATS

COMPOUND	ORAL LD_{50} (MG./KG.)		DERMAL LD_{50} (MG./KG.)	
	MALES	FEMALES	MALES	FEMALES
Aldrin	39*	60*	98*	98*
Chlordane	335*	430*	840*	690*
Chlorobenzilate	1040*	1220	–	–
DDA+	740*	600	–	–
DDE+	880*	1240*	–	–
DDT	113*	118*	–	2510*
Dieldrin	46*	46*	90*	60*
Dilan	–	–	6900*	5900*
Endrin	17.8*	7.5*	–	15*
Heptachlor	100	162	195	250
Isodrin	15.5*	7.0*	35*	23*
Kelthane	1100*	1000*	1230*	1000*
Lindane	88	91	1000	900
Methoxychlor	(6000.0)**	–	–	> 6000*
Perthane	> 4000*	> 4000*	–	–
TDE (DDD)	(3400)**	–	–	–
Thiodan	43	18	130	74
Toxaphene	90*	80*	1075	780

*These values were determined by the Toxicology Section under standardized conditions.

** Sex not specified.

+ Metabolite of DDT.

strated in milk and urine. The compounds stored in the fat are eliminated only very gradually when further dosage is discontinued.

Laboratory Findings: Laboratory findings are usually negative and always nonspecific except that the insecticide or its derivatives may be demonstrated in stomach contents, urine, or tissues, especially fat. See Appendices B and D.

Pathology: In experimental animals killed by large doses of chlorinated hydrocarbon insecticides, dilatation of blood vessels and even small petechial hemorrhages secondary to convulsions may be encountered. The outstanding changes following repeated DDT feeding in rodents are found in the liver. These changes consist of centrolobular hypertrophy, margination of cytoplasmic granules, fatty infiltration, and lipospheres formed by proliferation of smooth-contoured endoplasmic reticulum. Similar changes occur in combination following exposure to other chlorinated hydrocarbon insecticides and occur separately following a wide variety of toxicants. These changes have not been found in the higher animals nor in man. All species show liver cell necrosis but only at very high levels of dosage. Here again the changes are in no way specific.

Differential Diagnosis: Nervous symptoms and convulsions entirely similar to those of chlorinated hydrocarbon insecticide poisoning may be induced by a variety of economic poisons as well as by even less specific neurologic disease. If maximal symptoms are not reached within a matter of a few hours after acute exposure, then another diagnosis or some complicating factor should be sought. Even if it is known that an insecticide has been taken, the effect of the solvent should be carefully considered. (See section on solvents, page 114.)

Treatment: Depending on the condition of the patient, attention should first be given to sedation or to the removal of poison which may have been taken internally. Syrup of ipecac, gastric lavage, and saline laxatives may be used. Oil laxatives should be avoided, for they promote absorption of these insecticides and of many organic solvents. Removal of poison from the skin is important also; it is done best with soap and water.

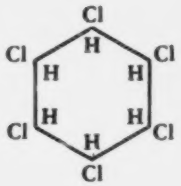
While antidotes discovered in animal tests can be expected to provide protection for poisoned human beings, it is not always easy to draw conclusions regarding human dosage from such tests. In general, the dosage of antidotes employed successfully in animals exceeds that considered safe in human practice. The following recommendations are necessarily based on the results obtained from the administration of likely antidotes to warm-blooded animals (including monkeys) previously dosed with lethal amounts of insecticide:

> Phenobarbital, which has been used in doses up to 0.7 g. per day in epilepsy, and pentobarbital (0.25 to 0.5 g.) are the barbiturates known to control convulsions of central origin. The object of sedation is not to induce sleep but to restore a relative calm; however, the proper dosage in the presence of poisoning may be so large that it would induce anesthesia if poisoning were not present.
>
> Calcium gluconate has been used less than the other antidotes. It is reported to control convulsions caused by chlorinated hydrocarbon insecticides in experimental animals, and it has seemed helpful in a few human cases. Since its mechanism of action is entirely different, it may be used in addition to sedatives.
>
> Epinephrine is contraindicated. It sensitizes the heart, predisposing to serious arrhythmias and thus to death.

BHC

Chemical Name: 1,2,3,4,5,6-hexachlorocyclohexane.*

Chemical Formula:



Formulations: In addition to the technical grade material,* solutions, emulsions, wettable powders, dusts, and poison baits are available. Lindane* is used in many formulations, especially those for household use.

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* The commercial product has about the following isomeric composition: alpha, 65% to 70%; beta, 6% to 8%; gamma, 12% to 15%; delta, 2% to 5%; epsilon, 3% to 7%; other isomers and related compounds, 2% to 3%.

Uses: BHC is widely used in the control of cotton insects. As a 1% powder lindane is used for the control of body lice which are resistant to DDT. BHC has been used for the control of other insects of public health importance particularly in the countries under British influence, and it has found some use for this purpose in the United States. Some household preparations contain BHC or lindane, and it has been used to some extent for the control of DDT-resistant flies and mosquitoes. In some areas, lindane is extensively used for termite control.

Routes of Absorption: BHC may be absorbed through any portal including the skin. The material is a local irritant, but this property is inversely proportional to the purity of the sample.

Pharmacologic Action: The several isomers of BHC have different actions. The gamma and alpha isomers are stimulants to the central nervous system, the principal symptom being convulsions. The beta and delta isomers are depressants of the central nervous system.

Dangerous Single Dose to Man: The dangerous single dose of the technical mixture has been estimated at about 30 g. and the dangerous dose of lindane at about 7 to 15 g. These estimates may be too high, for a young man suffered serious illness including a convulsion following a single carefully-measured dose of 45 mg. of lindane intended as a vermifuge. He was one of 15 patients treated with a highly dispersed emulsion at an intended dosage of 45 mg. (30 mg. for the last of the series) three times a day for 3 days. Of the 15 patients, 6 showed some toxic symptoms. It is true, that in similar studies of the potential use of benzene hexachloride as a drug, other persons have withstood larger doses, especially of undissolved or poorly dispersed material, apparently without serious effect. These observations are summarized in the table below. In these studies, it was found that a mixture of isomers burned the tongue and the unpurified mixtures were highly irritative.

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* Lindane is the accepted common name for essentially pure gamma isomer of benzene hexachloride.

The fatal poisoning of a 5-year-old girl weighing about 55 pounds was caused by the accidental ingestion of 4.5 g. of BHC as a 30% solution in an unspecified organic solvent. This represents a dosage of 180 mg./kg. In spite of evacuation of her stomach and therapy to restore failing circulation, she died.

Formulation (Percent Gamma Isomer)	Dosage	Effect
10-30	40 mg./day, 10 days	Diarrhea after 8th day.
60-85	40 mg./day, 14 days	No effect observed.
	110 mg./day, repeated	Diarrhea after 6th day.
100	40 mg./day, 14 days	No effect observed.
	45 mg. t.i.d., 3 days, (20 patients)	No effect observed.
	180 mg./day, repeated	Dizziness and diarrhea after several days.

A number of children have been poisoned by eating as little as a part of one (0.33 g.) tablet of lindane intended for use in thermal vaporizers. At least three 1.4 to 1.5-year-old children have been killed by eating larger amounts of lindane intended for this purpose. The dosage in one case was thought to be 7 g. In one other case, it was an unknown multiple of 0.8 g. (the weight of one tablet).

The use of thermal vaporizers with lindane has caused some clear-cut instances of respiratory poisoning. For example, two refreshment stand operators suffered severe headache; nausea; and irritation of eyes, nose, and throat shortly after exposure to lindane vapors from a dispenser in which the insecticide apparently became overheated. The symptoms abated 2 hours after the device was removed. Overheated lindane is more apt to cause respiratory distress than is lindane vaporized at lower temperatures. This is true because the greater heat releases more of the compound and also causes some splitting of the molecule into highly irritating decomposition products.

It is interesting to note that lindane shows a marked difference in toxicity to different species. Its toxicity to laboratory animals is less than that of DDT, but for several domestic animals, notably calves, lindane is more toxic than DDT or even dieldrin.

Dangerous Repeated Dose to Man: There are no confirmed cases of systemic poisoning in man as a result of repeated exposure to BHC.

It is interesting to note that in laboratory animals the gamma isomer has by far the greatest acute toxicity, but its relatively rapid excretion by the kidneys does not permit extensive accumulation in the body, and the gamma isomer shows the lowest toxicity on repeated exposure. The highest toxicity following repeated dosage and the lowest acute toxicity are shown by the beta isomer, which has no insecticidal importance but forms a part of those formulations prepared from technical grade BHC. The use of lindane, therefore, is favored not only because it is the most effective form of BHC for killing insects, but also because it probably presents a relatively low toxicity to workers who have long, intensive exposure.

Dermatitis and perhaps other manifestations based on sensitivity have been observed in human beings. Dermatitis has been reported in workers who came in contact with BHC and its precursors during manufacture without proper hygienic precautions.

Shortly after a lindane vaporizer was installed in her place of employment, a 35-year-old woman developed urticaria. The dermatitis improved during weekends, but recurred when she returned to work. Patch tests were positive. Complete elimination of exposure resulted in permanent recovery. For a more extended discussion see articles by the A.M.A. Committee on Pesticides: Health hazards of electric vaporizing devices for insecticides. J.A.M.A. **149**: 367-369, May 1952; Health problems of vaporizing and fumigating devices for insecticides; a supplementary report. J.A.M.A. **152**: 1232-1234, July 1953; and Abuse of insecticide fumigating devices, J.A.M.A. **156**:607, October 1954.

The threshold limit value for lindane in air is 0.5 mg./M^3.

Signs and Symptoms of Poisoning in Man: In 3 of the fatal cases, symptoms began 1 to 2 hours and death followed 12 hours or less after BHC was ingested. In another case, symptoms began 3.3 hours and death occurred 80 hours after ingestion. Illness was characterized by repeated, violent, clonic convulsions, sometimes superimposed on a continuous tonic spasm. Respiratory difficulty and cyanosis secondary to the convulsions were common. In some cases, the victim screamed during convulsions as if in terrible pain. In at least one case, the rectal temperature reached 103° F. Insofar as records are available, heart and respiratory failure appeared to be simultaneous. In the nonfatal cases, signs of hyperirritability have differed only in degree.

Men acutely exposed to high air concentrations of lindane and its decomposition products show headache, nausea, and irritation of eyes, nose, and throat.

Urticaria has followed exposure to lindane vapor in rare instances. Unlike the signs and symptoms already mentioned, this allergic manifestation occurs only in susceptible individuals, apparently only after a period of sensitization.

Blood dyscrasias have been attributed to BHC rarely. However, they probably have been attributed more frequently to it than to any other modern pesticide including those used in greater tonnage. About half the reported cases happened in one European country. It is possible that the occurrence of traces of impurities or some other differences of formulation account for the peculiar distribution of alleged cases. The same may be said about cases of nervous disorder in men working with BHC in another European country. The relationship between these disorders of the blood and the nervous system and BHC is not fully established even in connection with large doses.

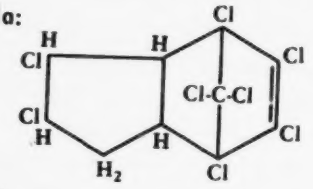
Laboratory Findings: In one case, the following concentrations of lindane were found at autopsy: fat, 343 ppm; liver, 88 ppm; stool, 478 ppm; and stomach contents, 105,000 ppm.

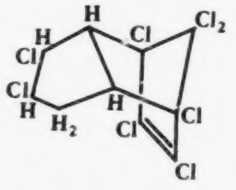
Pathology: In the case of a 1.5-year-old boy who ingested lindane with no solvent or other toxicant present, the gross findings included congestion of the lungs and kidneys, distention of the intestinal tract, and a reddish yellow appearance of the liver. Microscopically, the lungs showed edema, congestion, and bronchopneumonia. The liver exhibited fatty metamorphosis, and the kidney tubules revealed degenerative changes. There were tiny hemorrhages in the brain associated, at least in some instances, with necrosis in the walls of the small blood vessels. The change in the lung appeared to be consistent with aspiration pneumonia. The liver changes were more prominent than those seen in laboratory animals under similar conditions. The findings were similar in two other cases in which pathology was reported.

Chlordane

Chemical Name: 1,2,4,5,6,7,8,8-octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindane.*

Chemical Formula:





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* The technical grade chlordane consists of the A and B chlordane, heptachlor, and trichlor in addition to related materials and a small percentage of hexachlorocyclopentadiene.

Formulations: Chlordane is commercially available as wettable powders, emulsifiable concentrates, oil solutions, low percentage dusts, and technical chlordane. Technical chlordane is available in two grades – refined and agricultural. Both grades appear essentially equal in their insecticidal properties. The agricultural grade may be used wherever the staining of treated surfaces is not a problem. The refined grade is generally used for the control of household insect pests.

Uses: Chlordane has been found useful in agriculture. It was used rather extensively for control of flies and mosquitoes in Italy, Sardinia, and Greece until resistance developed. It is found in a number of household formulations sold in this country, either alone or in combination with other insecticides.

Routes of Absorption: Chlordane is readily absorbed through the skin as well as through other portals.

Pharmacologic Action: Chlordane is a stimulant to the central nervous system; its exact mode of action is unknown. Animals poisoned by this and related compounds show an extremely marked loss of appetite about the same time that they show neurological symptoms. See also page 47.

Dangerous Single and Repeated Doses to Man: Convulsions followed by recovery occurred in an infant following a dosage of about 10 mg./kg. and in an adult following 32 mg./kg. The fatal dose for man has been estimated to be between 6 and 60 g., and clinical experience indicates that this is essentially correct. One person receiving an accidental skin application of 25% solution amounting to something over 30 g. of technical chlordane developed symptoms within about 40 minutes and died before medical attention was obtained. In one patient known to be an alcoholic, death followed exposure to a low oral dosage of chlordane (2-4 g.). Microscopic examination of the tissues revealed severe chronic fatty degeneration of the liver, characteristic of chronic alcoholism. Although this fatality cannot be attributed exclusively to chlordane, it is consistent with previous observations that the toxicity of some chlorinated hydrocarbons is much enhanced in the presence of chronic liver damage.

A woman who ingested 6 g. (104 mg./kg.) of chlordane in talc with suicidal intent suffered chemical burns of the mouth, severe gastritis, enteritis, diffuse pneumonia, lower nephron syndrome, and central nervous system excitation with terminal mania and convulsions. Death occurred after 9.5 days. The most important autopsy findings were those of severe necrotizing bronchopneumonia, and desquamation and degeneration of the renal tubular epithelium. The dangerous repeated dose is unknown. The threshold limit value for chlordane in air is 2.0 mg./M^3.

Signs and Symptoms of Poisoning in Man: One person poisoned by chlordane developed convulsions within 40 minutes of gross skin contamination and died, apparently of respiratory failure, before medical aid could be obtained. Convulsions and coma may begin as little as 30 minutes after ingestion, but these signs do not preclude complete recovery.

Acutely poisoned experimental animals show similar signs. Experimental animals exposed to repeated small doses exhibit hyperexcitability, tremors, and convulsions, and those which survive long enough show marked anorexia and loss of weight. Symptoms in animals frequently occur within an hour of the administration of a large dose, but death often is delayed for several days depending on the dosage and route of administration. In any event, symptoms are of longer duration with chlordane than with DDT under similar conditions.

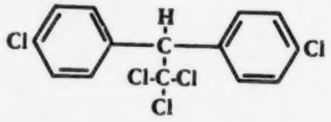
Laboratory Findings: See page 48.

Pathology: See page 48.

DDT

Chemical Name: 2,2,*bis*(*p*-chlorophenyl)1,1,1-trichloroethane.

Chemical Formula:



Formulations: DDT is available as a technical grade material, as emulsifiable concentrates of 50% or less, as wettable powders of 25% to 75%, as aerosol bombs, as solutions, as emulsions, and as dusts of various concentrations. Emulsions and wettable powder suspensions of 5% are commonly used in residual spray operations. Dusts frequently contain 10% of DDT. Many commercially available formulations contain, in addition to DDT, a variety of other insecticides and one or more solvents or carriers. Increasing use is being made of various synergists in combination with DDT to overcome the resistance developed to it by some insects. Many household insecticide sprays consist of a 5% solution of DDT in purified kerosene. All the ingredients of these preparations contribute to their toxicity.

Uses: DDT is probably the most widely used insecticide now available. It is used for a variety of purposes in agriculture, for the control of insects of public health and pest significance, and for various household uses. A 10% dust is employed for the control of human lice. Because of its very wide use, DDT is more likely to be encountered than any other single insecticide.

Routes of Absorption: DDT is absorbed from the intestinal tract and, if it occurs in the air in the form of a very fine aerosol or dust, it may be taken into the alveoli of the lung from which it is absorbed readily. DDT is not, however, absorbed through the skin unless it is in solution. Solutions are absorbed through the skin and, by the same token, emulsions are absorbed to some extent.

Likewise, fats and oils from whatever source increase the absorption of DDT by the intestine.

Pharmacologic Action: See page 47.

Dangerous Single Dose to Man: The oral dosage of DDT necessary to produce illness in man has become rather accurately known. A single ingestion of 10 mg./kg. produces illness in some but not all subjects, even though no vomiting occurs. Smaller dosages generally produce no illness, although a dosage of 6 mg./kg. produced perspiration, headache, and nausea in a man who was already sickly and who was hungry at the time of eating the compound. Those who have shown illness following ingestion of 10 mg./kg. have not shown convulsions. Convulsions have frequently occurred when the dosage level was 16 mg./kg. or greater. Dosages at least as high as 285 mg./kg. have been taken without fatal result. However, even somewhat smaller dosage levels lead to prompt vomiting, so that the amount retained is not determinable. After a single dose, the excretion of DDA in the urine reaches its height within a day or two and continues at a lower level for several days thereafter.

Animal studies indicate that DDD and Perthane are somewhat less toxic than DDT. Methoxychlor is significantly less toxic than DDT.

Dangerous Repeated Dose to Man: The minimal daily dosage producing illness in man is not known. Experiments with the most susceptible animals would suggest that some individuals might show mild illness at a dosage ranging from 2.5 to 5 mg./kg./day. Although dogs withstand 10 mg./kg./day for years without any adverse effect, the fact that some human subjects are made ill by a single dose at this rate shows that man is more susceptible to DDT than the dog. In studies of volunteers, 40 ate 35 mg. per man per day (about 0.5 mg./kg./day), 17 for as long as 21 months, without producing any adverse effect. A dosage of 0.5 mg./kg./day is about 200 times the daily rate at which the average citizen in the United States receives DDT in his diet. These volunteers on the higher dosage level stored from 101 to 466 ppm of DDT after 12 months and 105 to 659 ppm after 21 months. Periodic physical and laboratory examinations revealed no indication of any clinical effect of the DDT. An average concentration of about 50 ppm of DDT in the total dry diet would be required to produce a dosage of 0.5 mg./kg./day. The actual concentration of DDT in prepared meals is in the order of 0.25 ppm (dry basis), and the consequent dosage is calculated to be about 0.0026 mg./kg./day.

This dietary DDT is undoubtedly the major source of DDT and DDE stored in the fat of persons in the general population. Essentially all samples from people in the United States show some storage. The highest concentrations of DDT-derived material stored in anyone in recent years with no known occupational exposure were: DDT, 16 ppm; DDE, 31 ppm. The average storage level for DDT is less than 10 ppm and for DDE less than 15 ppm.

A higher content of DDT and its derivatives was found in workers who had occupational exposure. Even concentrations of DDT as high as 648 ppm and of DDE as high as 434 ppm in the fat of a man who had formulated DDT for 5 years were not associated with any detectable injury from DDT. Careful hospital examination of the workers who had very extensive exposure and who volunteered for examination revealed no abnormality which could be attributed to DDT. Much higher levels than have been found in man have been observed in the fat of experimental animals which were apparently asymptomatic.

DDT stored in the fat is eliminated only very gradually when further dosage is discontinued.

The threshold limit value for DDT in air is 1.0 mg./M^3.

Signs and Symptoms of Poisoning in Man: In acute poisoning, the time of onset depends on the dose; it may be as little as 30 minutes after a dose of 20 grams, but is usually 2 to 3 hours, and may be even longer. The onset is characterized by paresthesia of the tongue, lip, and part of the face. In more severe poisoning, the paresthesia may also be detected in the extremities, the proximal extent of the involvement depending on dosage. The patient soon suffers from a sense of apprehension, a disturbance of equilibrium, dizziness, confusion, and – most characteristic – tremor. In severe poisoning, convulsions may intervene, and there may be paresis of the hands. General symptoms include malaise, headache, and fatigue. Very large doses are followed promptly by vomiting, which apparently depends on an irritant action of the compound. Delayed vomiting with or without diarrhea may also follow, but the mechanisms of these actions are not clear. Careful medical examination during the period of severe symptoms indicates that the pupils are dilated. Except in severe poisoning the pupils react normally to light and accommodation, and the eyes show no nystagmus. Sensitivity to touch and pain are exaggerated in the areas in which the patient feels paresthesia, and proprioception and vibratory sensation may be lost in the fingers and toes but not in the more proximal portions of the arms and legs. Tests to demonstrate coordination are performed poorly, but the reflexes are normal except when the dosage has been very large. The pulse may be quickened in mild poisoning, probably as a nonspecific reaction to discomfort and apprehension. The pulse is irregular or abnormally slowed (45-60/min.), or both, in severe poisoning. Blood pressure and temperature remain essentially normal. Transient jaundice following a dosage of about 70 mg./kg. was reported by one observer but has not been seen by others even with higher dosage levels. Except in the most serious cases, recovery has always been well advanced or complete in 24 hours. Three persons, who were estimated to have eaten 20 g. of DDT each, still showed a residual weakness of the hands after 5 weeks.

There is no well-described case of fatal, uncomplicated DDT poisoning. In one instance, death followed the taking of an unstated amount of DDT powder with suicidal intent, but the possible involvement of other poisons was not excluded. A number of deaths have been reported following the ingestion of DDT solutions. In these instances, the clinical picture has frequently been characteristic of solvent poisoning.

Signs and symptoms of chronic poisoning in man are unknown, although, judging from experimental animals, liver and kidney dysfunctions should be looked for as possible complications of a disease entirely similar to acute poisoning.

The primary irritancy of DDT to the skin is practically nil, and it has little or no tendency to produce allergy. Dermatitis associated with DDT has occasionally been reported. Some cases involved physical irritation by flying chips, but local or systemic allergy should be expected to occur in rare instances, and the possibility should be considered and carefully studied. In no case should a dermatitis or other disease of allergic origin be ascribed to DDT without a careful effort to rule out other causes and without some direct demonstration that DDT is, in fact, involved.

Laboratory Findings: Laboratory findings are essentially negative except for the presence of DDT and its metabolites, which may be quantitatively measured by special methods. In any cases of acute DDT poisoning, the urine should be examined for the presence of DDA [*bis*-(*p*-chlorophenyl) acetic acid] (See Appendix D). Following the ingestion of a single dose of DDT at the rate of 11 mg./kg., the highest concentration of DDA reached in the urine of a volunteer was 2.24 ppm. Daily ingestion of DDT at the rate of 0.05 mg./kg./day for 270 or more days produced concentrations of 0.02 to 1.98 ppm, while 0.5 mg./kg./day gave 0.36 to 10.56 ppm of DDA. The single available report indicates a high concentration of DDT in human organs (but not necessarily fat) following fatal poisoning.

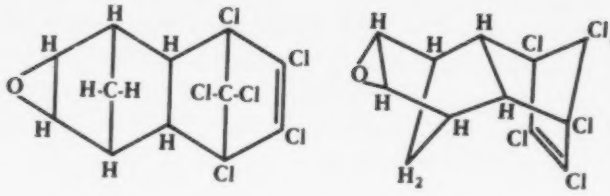
Pathology: See page 48.

Dieldrin

Chemical Name:

1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-*endo*,*exo*-5,8-dimethanonaphthalene.

Chemical Formula:



Formulations: Dieldrin formulations are available as wettable powders (25% to 75%), dust concentrates (25% to 50%), emulsifiable concentrates (18%), solutions (0.5%), impregnated pellets (1% to 15%) and as low percentage dusts (alone or in combination with other insecticides).

Uses: Dieldrin has been used extensively since 1952 for the control of a variety of agricultural insects and forest pests, especially in situations where a long-lasting residual effect is advantageous. It also has been used in several foreign countries as a residual house spray for control of disease vectors, but has been registered for limited treatment only of homes in this country to control some household pests. Dieldrin also is of value in the control of several species of mosquitoes, ticks, chiggers, and sand flies.

Routes of Absorption: Dieldrin is absorbed readily through the skin as well as through other portals.

Pharmacologic Action: Dieldrin like many other chlorinated hydrocarbons acts as a stimulant to the central nervous system; see page 47. Three syndromes (determined largely by the size and number of doses) may be recognized: (1) A few large doses produce increasing stimulation of the central nervous system culminating, if the dosage is sufficiently high, in one or more convulsions. If death does not occur, there is relatively prompt recovery without significant weight loss or other permanent injury. (2) A larger number of moderate-sized doses may produce without warning a condition marked by complete loss of appetite, weight loss, and convulsions. Without treatment, death is apparently inevitable. (3) Many relatively small doses may produce one or a few convulsions with lesser accompanying symptoms that may recur even though exposure is discontinued. Types 1 and 3 have been observed repeatedly in man; the occurrence of type 2 in man is unconfirmed, although it is easily produced in animals. Electroencephalograms indicate injury to the brain stem.

Dangerous Single Dose to Man: Those persons with the greatest opportunity for exposure to dieldrin may also have contact with related compounds, notably aldrin. The effects of dieldrin and aldrin are similar both quantitatively and qualitatively in animals, and this appears to be true for man also. Persons exposed to oral dosages which exceed 10 mg./kg. frequently become acutely ill. A dosage of about 44 mg./kg. led to convulsions in a child. Symptoms may appear within 20 minutes, and in no instance has a latent period of more than 12 hours been confirmed in connection with a single exposure.

The most thoroughly described related case involved an attempted suicide by ingesting aldrin at an estimated dosage of 25.6 mg./kg. There have been at least two deaths caused by the ingestion of undissolved dieldrin and several caused by drinking emulsions or solutions. The dosage in these cases is unknown.

In animals, the acute dermal toxicity of dieldrin in xylene is roughly 40 times that of DDT. Tests with certain other solvents indicate a factor of only about six. An important difference is that undissolved DDT is not absorbed from the skin but undissolved dieldrin is readily absorbed.

Dangerous Repeated Dose to Man: Little is known quantitatively about the toxicity of repeated doses of dieldrin for man. However, in different countries 2% to 40% of men applying 0.5% to 2.5% suspensions or emulsions at the rate of about 1 g./M^2 have developed poisoning within 2 weeks to 24 months after first exposure. Most of the cases were not complicated by contact with insecticides closely related to dieldrin. Some of the men were exposed to no other insecticide while some were previously exposed to DDT, BHC, or chlordane. However, no relevant disease has been reported following similar exposure to these latter three compounds alone or in combination.

Animals have shown convulsions as much as 120 days following the last dermal dose of dieldrin, indicating that dieldrin or its derivatives and/or residual toxicant-induced injury may persist in the body for a long time once severe poisoning has occurred. Entirely similar recurrent illness has been observed repeatedly in man.

The threshold limit values for aldrin and dieldrin in air are each 0.25 mg./M^3.

Signs and Symptoms of Poisoning in Man: Early symptoms of acute poisoning include headache, nausea, vomiting, general malaise, and dizziness. With more severe poisoning, clonic and tonic convulsions ensue or they may appear without the premonitory symptoms just mentioned. Coma may or may not follow the convulsions. Hyperexcitability and hyperirritability are common findings. Following repeated exposure some spraymen developed a condition indistinguishable from epilepsy – the number of cases being much greater than could be explained on the basis of idiopathic disease. Seizures recurred in some men even though they were removed from exposure. Poisoning characterized by a combination of convulsions, complete loss of appetite, and severe weight loss has not been confirmed in man but would probably occur under certain conditions of exposure. About 6 hours after ingesting dieldrin, a baby suddenly lost consciousness, became dyspneic and then convulsed. Finally the convulsions were stopped by treatment, but she remained unconscious; the temperature rose to 104° F., cyanosis and tachycardia increased, and the child died 20 hours after exposure.

Aldrin is reported to have caused erythemato-bullous dermatitis in a single case.

Laboratory Findings: Findings may be essentially normal except for the EEG, the presence of insecticide in the tissues, and the excretion of dieldrin-derived material in the urine. However, the mere finding of insecticide is not proof of poisoning, for the compound or derivatives have been demonstrated in the blood and urine of spraymen who were asymptomatic. To be sure, there was a general parallelism in the results of bioassays on blood and the presence of poisoning; workers who had had convulsions tended to show high concentrations of dieldrin in their blood.

Aldrin absorbed into the body is converted to dieldrin and stored in that form. In one case of acute aldrin poisoning with complete recovery, dieldrin was found in the fat in a concentration of 40 ppm. Earlier reports based on older analytical methods indicated lower concentrations in other cases.

In the case in which aldrin was ingested at the estimated rate of 25.6 mg./kg., laboratory tests indicated transient kidney damage and questionable liver involvement. The patient responded well to supportive therapy and showed no residual effects except for border-line abnormalities of the electroencephalogram. Later electroencephalographic studies of a series of patients showed specific changes: bilateral synchronous spikes, spike and wave complexes, and slow theta waves.

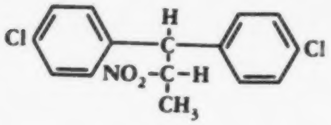
Treatment: In addition to the information on page 49, the following is of importance. Animal experiments indicate that it maybe necessary to give phenobarbital in large doses over a period of 2 weeks or more in connection with the syndrome characterized by complete loss of appetite and severe weight loss. The dosage required to keep poisoned animals from showing hyperexcitability or convulsions and to enable them to eat and behave normally is often a dosage that would induce sleep or even anaesthesia in a normal animal of the same species. In human beings the dosage should be adjusted to the symptoms.

Prevention: Workers applying dieldrin residual sprays indoors or workers who are otherwise exposed extensively to dieldrin for relatively long periods of time should be told clearly about the danger which carelessness may involve. They should be thoroughly trained in proper methods of handling dieldrin, and they should be provided with industrial safeguards or protective clothing suitable to the conditions of work. Work should be limited to 40 hours per week. Periodic electroencephalographic examinations may offer a valuable method for detecting subclinical intoxication.

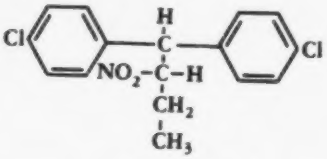
Dilan

Chemical Name: mixture of 2-nitro-1,1-*bis* (*p*-chlorophenyl) propane (1 part) plus 2-nitro-1,1-*bis* (*p*-chlorophenyl) butane (2 parts).

Chemical Formula:



2-nitro-1,1-*bis*
(*p*-chlorophenyl) propane
Prolan (1 Part)



2-nitro-1,1-*bis*
(*p*-chlorophenyl) butane
Bulan (2 Parts)

Formulations: Dilan is available as an 80% liquid concentrate, and as dusts.

Uses: Dilan has been recommended for use in fly control for strains resistant to other chlorinated hydrocarbons. (Following spraying directly on skin of cattle, Dilan is excreted in milk in amounts intermediate between DDT and methoxychlor and, therefore, is not recommended for use on dairy cattle.)

Dilan is used to some extent as a substitute for pyrethrum powder in control of agricultural pests.

Routes of Absorption: Toxicity tests in lower animals indicate that it can be absorbed from the digestive tract. Dilan does not seem to be absorbed to an appreciable extent through the skin.

Toxicology: In the absence of reported poisoning, the dangerous dose to man is unknown. Results with animals indicate that the mixture is considerably less toxic than DDT. In animals, the signs and symptoms resemble those caused by the other chlorinated hydrocarbons.

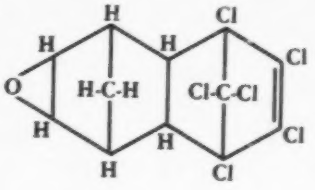
Laboratory Findings: None available.

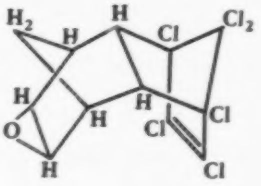
Treatment: See page 49.

Endrin

Identity: 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-*endo-endo*-5,8-dimethanonaphthalene.

Formula:





Fomulations: Endrin is available as dusts (1.5%), granules (1%), water-wettable powders (as high as 75%), emulsifiable concentrates (19.5%) and baits (0.75%).

Uses: Endrin is used for soil insects and foliage insects (with limitations to prevent residues in the food of man or animals); it is also used for seed treatments and for the control of mice in orchards.

Phamacologic Action: See dieldrin, which has the same action.

Routes of Absorption: Endrin is absorbed by the skin as well as by the respiratory and gastrointestinal systems.

Dangerous Single and Repeated Doses to Man: An outbreak of poisoning was caused by the contamination of sacked flour during shipment in a railway car in which endrin had leaked two months earlier. Endrin in a concentration of 150 ppm was found in the remains of a loaf of bread that had caused illness in one person. The severity of illness was proportional to the amount of bread eaten; 3 or 4 slices or 2 or 3 rolls were usually sufficient to produce a convulsion, and a man who ate nearly a whole loaf had repeated convulsions in quick succession for about an hour. Computations based on these observations indicate that the dosage necessary to produce a single convulsion in man is about 0.20 to 0.25 mg./kg., and the dosage necessary to produce repeated fits probably is about 1 mg./kg. A child who died an hour and 10 minutes after ingesting endrin is estimated to have taken about 30 mg./kg. Animal experiments suggest that a much smaller dosage also could be fatal.

There is no direct evidence on the repeated dosage that must be absorbed in order to produce illness. Endrin poisoning has occurred among formulators and applicators. Endrin is more toxic than dieldrin and, by analogy, endrin would be expected to require somewhat smaller dosages to produce poisoning following daily exposure.

The tentative threshold limit value for endrin in air is 0.25 mg./M^3.

Signs and Symptoms of Poisoning in Man: In the contaminated bread episode, mild illness involved dizziness, weakness of the legs, abdominal discomfort, and nausea but usually not vomiting. Several patients were temporarily deaf, and some were slightly disoriented or aggressive. Insomnia was common. More serious illness involved convulsions and occurred in about 30 people. The time of onset was irregular, but usually 2 to 4 hours in those who ate contaminated bread only once. People who ate 2 or more meals frequently showed no acceleration of onset after the last dose, but in some instances onset was as little as half an hour after the meal. The fits were sudden and without warning. They were epileptiform in character with frothing at the mouth, facial congestion, and violent convulsive movements of the limbs, sometimes leading to dislocation of the shoulder or other injury. The fits lasting several minutes were followed by semiconsciousness for 15 to 30 minutes. Recovery was well advanced by the next day in most patients but a few complained of headache, dizziness, lethargy, weakness, and anorexia for 2 to 4 weeks. Except for abnormal electroencephalograms, neurological findings were normal soon after a convulsion.

In fatal cases, the onset may be as little as 20 minutes, and death about an hour after ingestion. Convulsions may become almost continuous. Hyperthermia (107°F. or more) was associated with endrin poisoning in two children, 1 and 2.5 years old. The high fever was followed by decerebrate rigidity in both instances. The hyperthermia may have been a specific effect of endrin. Other findings in one of the cases strongly suggested injury to the brain stem. The same conclusion is justified by electroencephalographic studies.

Laboratory Findings: The insecticide has been found in the fat of man (as high as 400 ppm by bioassay) and other tissues (as high as 10 ppm). The concentrations consistent with health or disease in man are not yet established. Electroencephalograms may show bilateral synchronous spikes, spike and wave complexes, and slow theta waves. The EEG usually returns to normal within 3 to 6 months after exposure is stopped.

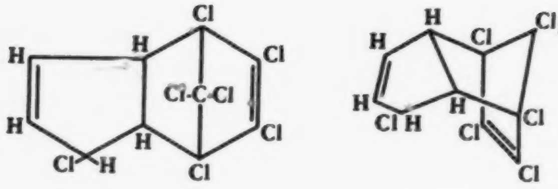
Treatment: See dieldrin, page 66.

Preventions: See dieldrin, page 66.

Heptachlor

Chemical Name: 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindane.

Chemical Formula:



Formulations: Heptachlor is available as emulsifiable concentrates (24%), 2.5% dusts, 25% wettable powders, and granular formulations containing from 2.5% to 25% heptachlor. Heptachlor is also formulated with some fertilizer mixtures for the control of soil pests.

Uses: Heptachlor is used against flies, mosquitoes, and a variety of household pests. It is also used in controlling agricultural pests, especially soil insects.

Toxicology: It has been estimated that the minimal dermal dose required to produce symptoms in man is 46 g. for a single dose and 1.2 g. per day for repeated exposure. In animals, heptachlor causes signs of poisoning similar to those caused by aldrin and dieldrin (see page 62). Just as aldrin is converted in the body to its epoxide (dieldrin), so heptachlor is converted to its epoxide and stored largely in that form.

The threshold limit value for heptachlor in air is 0.5 mg./M^3.

Laboratory Findings: See page 48.

Treatment: See dieldrin, page 66.

Toxaphene

Identity: A chlorinated camphene whose approximate empirical formula is $C_{10}H_{10}Cl_8$, representing a chlorine content of between 67% and 69%.

Formulations: Toxaphene is marketed as the technical grade material; as a 40% dust concentrate; as dilute dusts; as a wettable powder; as impregnated pellets; as 42% to 73% emulsifiable concentrates; as 44% to 80% concentrates in oil; as a 5% bran bait; and as a cotton dusting formula (toxaphene 20%, sulfur 40%, inert material 40%).

Uses: Toxaphene is used for the control of grasshoppers, soil pests, and many insects that attack forage crops, cotton, and certain vegetables. It is also used to control the ectoparasites of livestock.

Routes of Absorption: Toxic and in some instances lethal amounts of toxaphene can enter the body through the mouth, lungs, and skin. Enteric absorption of the insecticide is increased by the presence of digestible oils, and liquid preparations of the insecticide penetrate the skin more readily than do dusts and wettable powders.

Pharmacologic Action: In general, toxaphene resembles chlordane and to some extent camphor in its physiological action. Toxaphene causes diffuse stimulation of the brain and spinal cord resulting in generalized convulsions of a tonic or clonic character. Death usually results from respiratory failure. Detoxification appears to occur in the liver.

Dangerous Single and Repeated Doses to Man: Toxaphene has an irregular range of toxicity with the minimal acute lethal oral dose for man estimated to be 2 to 7 g. Its chronic oral toxicity in the dog (an animal susceptible to toxaphene) is some 10 times that of DDT. In man a single dermal application of 46 g. or daily applications of 2.4 g. over a period of days is very dangerous. Toxaphene causes moderate irritation of the skin but little or no sensitization.

At least 7 human deaths have been reported as due to toxaphene. All 7 cases were children. In 5 instances the poison was swallowed and may have been swallowed in the other cases also; the dosage could not be determined. From other cases, it appears that 10 mg./kg. or less leads to nonfatal convulsions in some persons but to no disease at all in other persons.

Signs and Symptoms of Poisoning in Man: Nonfatal poisoning generally begins in 4 hours or less after toxaphene is ingested. In fatal cases, severe symptoms have begun as early as half an hour after exposure, and death occurred in one instance in less than 4 hours from the time of exposure. In all reported cases, death has occurred or recovery has begun and been essentially complete in a period of 12 hours or less. However, control of convulsions is not necessarily decisive. In one case, convulsions had been controlled for some hours, and there were hopeful signs of improvement for a time, followed by a sudden rise in temperature, respiratory collapse, and death. Nonfatal poisoning has been characterized by nausea, mental confusion, jerking of the arms and legs, and by convulsions. In some instances convulsions have begun suddenly without any warning signs or symptoms. Fatal poisoning has been characterized by frequent, repeated, violent convulsions and by cyanosis. In some instances the cyanosis may result from mechanical interference of the convulsions with respiration. However, in one carefully observed case, cyanosis appeared before convulsions.

Laboratory Findings: The only significant finding is the storage of compounds related to toxaphene. This complex can be specifically identified.

Pathology: See page 48.

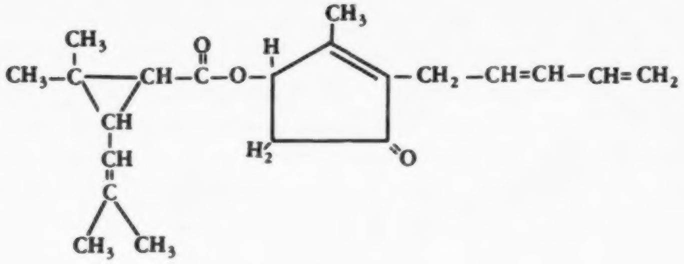
Treatment: See page 49.

BOTANICAL INSECTICIDES

Pyrethrum and Allethrin

Chemical Name: The active ingredients in pyrethrum extract consist of a mixture of four compounds, pyrethrin I and II, and cinerin I and II. Pyrethrin I, the constituent possessing the greatest insecticidal activity, is represented by the chemical formula shown below. Allethrin is a synthetic pyrethrin analogue.

Chemical Formula:



Formulations: Pyrethrum and allethrin are available commercially in powder or dust form, in a variety of solvent extracts, and in emulsifiable preparations of various concentrations. The usual household spray contains about 0.5% active pyrethrum principles.

Uses: Pyrethrum and allethrin, alone or combined with synergists, are used extensively in dusts, sprays, and aerosols against a wide variety of insects. Allethrin has also been used in vaporizers.

Routes of Absorption: Pyrethrum and allethrin may be absorbed from the gastrointestinal tract and by the respiratory route. They are not absorbed to a significant degree through the skin; however, allergic reactions may result from this route of exposure.

Pharmacologic Action: The nervous symptoms produced by pyrethrum and allethrin poisoning resemble those of veratrin intoxication, proceeding from excitation to convulsions to tetanic paralysis, except that pyrethrins cause muscular fibrillation as well. Death is due to respiratory failure. If recovery occurs, it is usually complete. Injury to man from pyrethrum has most frequently resulted from the allergenic properties of the material rather than its direct toxicity.

Dangerous Single and Repeated Doses to Man: Under practical conditions, pyrethrum and allethrin are probably the least toxic to mammals of all the insecticides currently in use. Pyrethrum has been used orally as an anthelmintic in some areas for many years with no apparent ill effects. The approximate oral LD_{50} to white rats of pyrethrum is 200 mg./kg. and of allethrin, 680 mg./kg.

The occurrence of a rare individual hypersensitive reaction, especially following a previous sensitizing exposure, is a possibility. The death of a two-year-old child following the eating of one half ounce (15 g.) of pyrethrum concentrate was attributed to pyrethrum poisoning. The esters constituting allethrin and pyrethrum mixtures are rapidly detoxified by hydrolysis in the gastrointestinal tract and to some extent in other tissues of warm-blooded animals. The chrysanthemum monocarboxylic acid formed is excreted in the urine. Because of their ready excretion, these compounds exhibit little or no toxicity following repeated exposure.

The threshold limit value for pyrethrum in air is 5 mg./M^3.

Signs and Symptoms of Poisoning in Man: Pyrethrum toxicity may manifest itself in several forms in man. Contact dermatitis is by far the most common. The usual picture is a mild erythematous, vesicular dermatitis with papules in moist areas, and intense pruritus. A bullous dermatitis may develop. Some individuals show manifestations of pyrethrum sensitivity similar to those seen in pollinosis, including sneezing, serous nasal discharge, and nasal stuffiness. A few cases of extrinsic asthma due to pyrethrum mixtures have been reported. Some of the individuals involved had a previous history of asthma with a very broad allergic background.

A severe anaphylactic reaction, including peripheral vascular collapse and respiratory difficulty, is a rare accompaniment of the dermatologic reaction.

Laboratory Findings: Positive patch tests with pyrethrum are helpful in diagnosis. Eosinophilia may accompany the acute allergic reaction. Examination of mucous nasal smears from individuals with vasomotor rhinitis reveals numerous eosinophils following exposure.

Treatment: The treatment for the various reactions to allethrin and pyrethrum is symptomatic. Antihistimines are of value. If sufficient pyrethrum has been ingested to cause nervous manifestations, pentobarbital should be used. The diarrhea that occurs may be controlled with atropine sulfate.

RODENTICIDES

Introduction: The rodenticides differ widely in their chemical nature. Strange to say, they also differ widely in the hazard which they offer under practical conditions, even though all of them are used to kill animals that are physiologically similar to man. Sodium fluoroacetate is one of the most hazardous rodenticides available. Warfarin is the most thoroughly studied of a group of new rodenticides which present a minimal hazard.

With the exception of arsenic, thallium, and phosphorus, the older rodenticides are not covered in this handbook, but their properties are listed in standard texts on pharmacology. (Arsenic is discussed under "Herbicides" because of its relative importance as an eradicative weed killer.)

Phosphorus

Identity: Elementary phosphorus occurs in two common forms: the relatively harmless red and the highly toxic white or yellow.

Formulations and Uses: White phosphorus is formulated as a 2% to 5% paste for use against rats and roaches.

Routes of Absorption: Poisoning results from ingestion. Contact of yellow phosphorus with the skin causes burns, but dermal absorption is not known to lead to systemic poisoning.

Dangerous Single and Repeated Doses to Man: A dose of 15 mg. may be severely toxic and 50 mg. may be fatal. The element is more toxic when ingested in solution or in a finely divided state than when taken in lumps. A daily dosage of 1 mg. given with therapeutic intent sometimes produced gastrointestinal disturbance, necrosis of the jaw, and rarely typical phosphorus poisoning. The threshold limit value for yellow phosphorus in air is 0.1 mg./M^3.

Signs and Symptoms of Poisoning in Man: Acute phosphorus poisoning is peculiar because symptoms appear in two stages. During the first 24 hours, symptoms of severe gastrointestinal irritation occur as soon as one-half hour after ingestion. The victim may die of cardiovascular failure within 12 hours. This first stage may be followed by a latent period lasting from a few hours to a few days depending upon the amount ingested. The systemic stage is characterized by abdominal pain, nausea, vomiting, hematemesis and other hemorrhagic manifestations, jaundice, hepatomegaly, oliguria, toxic psychosis, convulsions, coma, and shock. There may be severe damage to the liver, heart, and kidney, and death may ensue at any time. Cirrhosis of the liver has been reported after recovery from the acute state.

Formerly, chronic poisoning, characterized by necrosis of the mandible and maxillary bone, was caused by prolonged inhalation of phosphorus in industry.

Pathology: Fatty degeneration is striking in the liver, heart and kidney but may be found in all organs. Hepatic necrosis may be extensive with changes occurring first in the periphery of lobules.

Differential Diagnosis: If history of phosphorus exposure is unavailable, the initial symptoms may be confused with the gastroenteritis caused by agents such as arsenic. There is a characteristic odor of garlic to the breath and vomitus in phosphorus poisoning. Luminescence in a darkened room of the gastric contents, feces, or urine is pathognomonic.

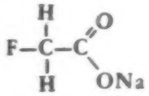
Laboratory Findings: Urinalysis may show albuminuria, cylindruria, and hematuria. Liver function tests, including prothrombin time, are abnormal. Hypoglycemia may be severe; blood urea nitrogen and creatinine may be elevated. The phosphorus content of the blood is usually normal. EKG changes may be present with myocarditis. Analysis for phosphorus may be done on tissue or gastric contents.

Treatment: Since there is no specific therapy, the removal of phosphorus by vomiting or gastric lavage with large volumes of fluid is of utmost importance. Potassium permanganate, 0.1% solution, or 2% hydrogen peroxide are used in preference to water since they may oxidize phosphorus to harmless phosphates. Two hundred ml. of mineral oil or 100 to 200 ml. of petrolatum, which prevents phosphorus absorption, can then be administered. However, absorption can be increased by other fats and oils. The treatment of shock and acute hepatic or renal failure is instituted when necessary. Adequate carbohydrate intake is important. Shock has responded to vasopressor agents. The use of steroids resulted in dramatic improvement in one case of severe poisoning after the ingestion of 825 mg. of phosphorus.

Sodium fluoroacetate

Chemical Name: sodium monofluoroacetate.

Chemical Formula:



$$\mathrm{F-\underset{H}{\overset{H}{C}}-C(=O)ONa}$$

Formulations: Sodium fluoroacetate is a colorless, odorless, water-soluble salt having a purity of about 95%. An extremely dilute solution has a vinegar-like taste, at least to some people. The salt is dissolved in water in the proportion of 12 g./gal. (1:300). This solution is used against rats by filling ¾-ounce squat souffle cups (70 mg./cup) and by placing these at strategic locations in rat-infested areas. This solution is often colored with a black dye. Sodium fluoroacetate is also mixed with common rat baits at the rate of 1 oz. of poison to 28 lbs. of bait (1:500).

Uses: Sodium fluoroacetate is a nonspecific poison which is used to kill rats, mice, other rodents, and predators in general.

Routes of Absorption: Sodium fluoroacetate is rapidly absorbed from the gastrointestinal tract. Oral doses of sodium fluoroacetate have approximately the same toxicity as those given subcutaneously, intramuscularly, intraperitoneally, or intravenously. Sodium fluoroacetate is not readily absorbed through the intact skin, but it may be absorbed in the presence of cuts or dermatitis. Dusts of the poison are efficiently absorbed in the pulmonary system. The poison appears to be uniformly distributed in the tissues, including the brain, heart, liver, and kidney.

Pharmacologic Action: Following absorption, sodium fluoroacetate appears to act without being chemically changed. Through a direct interference with acetate metabolism by an ill-defined mechanism, sodium fluoroacetate has a strong effect on either the cardiovascular or nervous system, or both, in all species and on the skeletal muscles in some species. Man gives a mixed type response with the cardiac feature predominating. By a direct action on the heart, notably in the rabbit, contractile power is lost, which leads to declining blood pressure. Premature ventricular contractions are seen in all species and arrhythmias are marked in some species including man. The central nervous system, notably that of the dog, is directly attacked by sodium fluoroacetate. In man, the action on the central nervous system produces epileptiform convulsive seizures followed by severe depression. Cumulation of sodium fluoroacetate occurs to some extent, and some tolerance can be demonstrated in the mouse and rat, and possibly in the rhesus monkey.

Dangerous Single Dose to Man: Judging from fatal and near-fatal cases, the dangerous dose for man is 0.5 to 2 mg./kg. Other species vary considerably in their response to sodium fluoroacetate with primates and birds being the most resistant and carnivora and rodents being the most susceptible. Most domestic animals show a susceptibility falling between the two extremes.

The threshold limit value for sodium fluoroacetate in air is 0.05 mg./M^3.

Signs and Symptoms of Poisoning in Man: In all species, there is a variable latent period ranging from 30 minutes to 2 hours or more between dosing and the appearance of symptoms. This period is shortened but not eliminated by large amounts of sodium bicarbonate, fumarate, or chloride. Both man and rhesus monkeys give a "mixed response" to fluoroacetate poisoning. In both fatal and nonfatal cases in man, the first indication of poisoning was nausea and mental apprehension, generally followed by epileptiform convulsions. After a period of several hours, *pulsus alternans* may exist followed by ventricular fibrillation and death. Children appear to be more subject to cardiac arrest than to ventricular fibrillation. In rhesus monkeys convulsive seizures pass from the facial muscles to the ear and masseter muscles and then over the entire body, ending in violent jerks. Recovery from the seizure may occur only to be followed by a sudden attack of ventricular fibrillation and cardiac failure.

Laboratory Findings: In animals, increases in the blood levels of certain constituents have been observed as follows: (1) glucose in rabbits and goats, (2) lactic and pyruvic acids in the rabbit, (3) acetate in the dog. Serum inorganic phosphate levels (probably from muscle) are increased in goats and rabbits; the concentration of plasma potassium is also increased (from control levels of 17 mg./100 ml. to 25 mg./100 ml.) in poisoned animals. Analyses for fluorine content of the organs of a fatally poisoned patient showed elevated values.

Pathology: The histopathologic changes in poisoning by fluoroacetate appear to contribute little to the elucidation of its action. Congestion of abdominal viscera and lungs, resulting from cardiac failure is seen in animals, with focal lung hemorrhage and generalized hemorrhage occurring in the rat and chicken, respectively.

Differential Diagnosis: In general, poisoning with sodium monofluoroacetate is so acute and so violent that it has only to be distinguished from poisoning with other convulsant poisons.

Treatment: The treatment for sodium fluoroacetate poisoning is mainly symptomatic. Immediate emesis and gastric lavage followed by oral doses of magnesium sulfate may be useful. Administration of certain compounds capable of supplying acetate ions have shown antidotal effects in animals including monkeys; the choice drugs being monoacetin (glycerol monoacetate) (0.1 to 0.5 ml./kg. by deep intramuscular injection). A single dose of magnesium sulfate

(800 mg./kg.) given intramuscularly as a 50% solution has saved the life of rats dosed with lethal amounts of sodium fluoroacetate. Complete quiet and rest are indicated, but barbiturates to the point of anesthesia have proved disappointing when used as antidotes against this poison.

Prevention: Sodium fluoroacetate should be used by competent specialists and then only under very strict limitations.

Thallium

Identify and Formula: thallium sulfate, $TlSO_4$.

Formulation and Use: Thallium sulfate is sold as the salt, as prepared rodenticides (0.5% to 3% food baits and 1.5% liquid baits) and as ant and roach poisons (0.05% to 3% baits). Some States and cities ban the general sale of formulations containing more than 1% or 2% thallium sulfate.

Routes of Absorption: The oral route is the most important in cases of poisoning, although dermal absorption may also occur. Formerly, intoxication but no known deaths resulted from the application of ointment containing 3% to 7% thallium acetate for depilation.

Pharmacologic Action: Thallium is a cellular toxin and resembles arsenic in its effects. However, sulfhydryl-containing enzymes are only slightly inhibited by thallium. Thallium is distributed to all the tissues of the body; there is no tendency to accumulate in bone. Excretion is mainly by the kidney and to some extent into the intestine. In humans, only about 3.2% of the thallium in the body is excreted each day.

Dangerous Single and Repeated Doses to Man: Thallium acetate was formerly used as a depilatory in children at a single oral dose of 8 mg./kg. Lower dosages were unreliable in causing hair loss. Depilation is, of course, a toxic effect. Even though dosage was carefully regulated, serious poisoning, including 6 deaths was found in 5.5% of 8,006 cases. No deaths were reported at lower dosages, but poisoning occurred in 1 case from a dose of 4 mg./kg. of thallium acetate. Adults are susceptible to lower dosages than children and thallium was administered therapeutically only to children under 10 or 12. Thallium acetate and sulfate are equivalent in toxicity; both compounds are water-soluble and contain about 80% thallium.

Thallium is a cumulative poison. The repeated dose necessary to produce toxicity is not so well known. The daily oral administration of thallium acetate to rats at less than 1/50 of the single LD_{50}-dose caused depilation in 6 weeks and death in rats within 4 months. The threshold limit for thallium in air in 0.1 mg./M^3.

Signs and Symptoms of Poisoning in Man: The clinical picture resembles arsenic intoxication. Signs and symptoms are referable mainly to the gastrointestinal tract and nervous system. After large doses, gastroenteritis is evident in about 12 to 14 hours, while neurological symptoms may be delayed 2 to 5 days. Gastrointestinal manifestations include severe paroxysmal abdominal pain, vomiting, diarrhea, anorexia, stomatitis, salivation, and weight loss. Neurological manifestations during the first days of illness may include paresthesias, headache, cranial nerve damage, convulsions, delirium, and coma. Vascular collapse and death may occur in 24 to 48 hours, but the course is usually more prolonged. Death may be caused by respiratory paralysis, pneumonia, or circulatory disturbances. Peripheral neuropathy, particularly in the legs, is common with severe pain, paresthesias, muscle weakness, and atrophy. Loss of hair begins after 1 to 2 weeks have elapsed. In the more protracted cases, ataxia, choreiform movements, dementia, depression, and psychosis may be prominent. A blue gingival line and dermatological abnormalities, including white bands in the nails may appear. Neurologic damage may be permanent. Liver damage occurs but is not prominent clinically. Kidney damage is manifested by proteinuria, cylindruria, and sometime oliguria and hematuria.

With the continued administration of smaller doses, symptoms may first be apparent in a week with progression for several more weeks. In chronic poisoning, symptoms can be nonspecific and thallium intoxication may not be suspected unless depilation occurs. Although characteristic of thallium toxicity, hair loss also can result from poisoning with other metals and certain drugs.

Laboratory Findings: Diagnosis can be confirmed by analysis for thallium in urine, blood, or hair. Thallium does not occur normally in body fluids or tissue; however, its presence in urine does not necessarily mean intoxication. In fatal, acute and subacute cases, the concentration of thallium in tissue ranges from 5 to 100 ppm. Thallium can be found in the urine for as long as 2 months after intoxication. Other laboratory determinations are not specific. The blood picture and the cerebrospinal fluid are usually normal. Tests of liver function have been abnormal in a few instances.

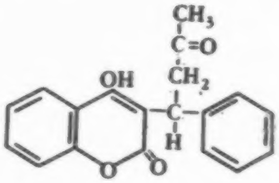
Pathology: Only hyperemia and punctate hemorrhages of the gastrointestinal tract and visceral congestion may be found if death is soon after exposure. There may be fatty degeneration of the heart and liver, degeneration of kidney tubules, and edema and congestion of the lungs. Degeneration occurs in peripheral nerves, and cortical vessels are engorged. Chromatolysis in neurones is prominent in the pyramidal tracts, basal ganglia, and third nucleus.

Treatment: Gastric lavage should be done in acute cases. Activated charcoal and potassium iodide can be given orally to reduce thallium absorption. Sodium thiosulfate may be given intravenously to inactivate any thallium in the blood, but its usefulness has not been proved. In one study, dithizon, a chelating agent, was effective in 5 out of 6 severely ill children in an oral dosage of 10 mg./kg. twice a day for 4 days or longer. The mechanism of action was unknown. It is generally felt that EDTA or BAL are not useful in the treatment of thallium intoxication. However, there are reports of improvement after the administration of BAL. In animals BAL has not been effective, while dithizon (diphenylthiocarbazone) was protective in rats after thallium administration. In one report, trihexyphenidyl (Artane) caused a striking reduction of tremors.

Warfarin

Chemical Name: 3-(α-phenyl-β-acetylethyl)-4-hydroxycoumarin. The compound is also available as the sodium salt.

Chemical Formula:



Formulations: Warfarin is available in the form of a 0.5% powder. The diluent is cornstarch suitable for mixing with additional bait such as corn meal, bread crumbs, meat, etc. A final concentration of 0.025% or less is recommended for bait, depending on the species of rodent to be controlled and upon other conditions. In addition to the concentrate, finished baits containing 0.025% warfarin are available commercially. Warfarin sodium is available pharmaceutically in capsules and tablets.

Uses: As a rodenticide, warfarin is used both for commensal rats and mice and for wild forms. It has proved to be very effective.

Routes of Absorption: Warfarin is readily absorbed by the gastrointestinal tract; absorption of the sodium salt in man requires about 3 hours as indicated by a comparison of the rate of action of oral and intravenous doses. Warfarin is not significantly absorbed through the skin. Its absorption by the respiratory tract is unknown, but there need be no circumstance in which small particles of dust could be inhaled, even in manufacture.

Phamacologic Action: Warfarin has two actions: inhibition of prothrombin formation and capillary damage. There is unconfirmed evidence that these two actions are produced by the two moieties of the molecule. Thus, 4-hydroxycoumarin inhibits the formation of prothrombin and reduces the clotting power of the blood, while there is some evidence that at sufficient dosage benzalacetone produces capillary damage and leads to bleeding upon the very slightest trauma. Significantly enough, vitamin K has an antidotal action against both actions of warfarin up to a certain point.

A single intravenous, therapeutic, dose of the sodium derivative (70-75 mg. or about 1 mg./kg.) in man may produce some increase in prothrombin time within 2 hours, and usually produces a substantial increase within 14 hours. The average maximum response is on the fourth day. Spontaneous recovery to normal occurs about 8 days after a single therapeutic dose. Thus, significant clinical depression of prothrombin level is maintained for 3-6 days. In the treatment of thromboembolic disease, a maintenance dose of about 10 mg./day or 50 mg. every 5 days is required to keep the prothrombin level between 10% and 30% of normal. Patients have been thus maintained for years.

All the pathology induced by warfarin is reversible up to a certain point (See below).

Warfarin and some other anticoagulants are derived from coumarin while others as well as the drug phenindione are indandione derivatives. The occurrence of agranulocytosis and hepatitis in some patients treated with phenindione suggests the possibility that phenindione compounds may have effects entirely unrelated to their anticoagulant properties.

Dangerous Single and Repeated Doses to Man: Serious illness was induced by the ingestion of 1.7 mg. of warfarin per kg. per day for six consecutive days with suicidal intent. This would correspond to eating almost 1 pound of bait (0.025% warfarin) each day for 6 days. All signs and symptoms were caused by hemorrhage and, following multiple small transfusions and massive doses of vitamin K, recovery was complete.

In Korea, a family of 14 persons lived for a period of 15 days on a diet consisting almost entirely of corn meal containing warfarin. The dosage of the different individuals was determined to vary from about 1 to 2 mg. of warfarin per kilogram per day. As a result of this exposure and without benefit of treatment, 2 of the 14 persons died. A 19-year-old girl who was in a state of shock and severe hemorrhage 2 days after the warfarin diet was discontinued recovered following a blood transfusion and small daily doses of vitamin K. The remaining 11 members of the family recovered within a week after exposure, although only small daily doses of vitamin K were given, and although they all had shown marked signs of poisoning when they first accepted treatment. Recovery of the 12 survivors was complete. The entire episode was made possible only by a series of unusual events and by the extraordinary apathy of the family, resulting in their totally ignoring unmistakable signs of illness.

The possibility of human poisoning by warfarin must be kept in mind. In spite of one reported case which suggests the possibility of hypersensitivity, the safety factors and experience with use of the sodium salt in medical treatment make it appear unlikely that poisoning with this pesticide will occur except with suicidal intent or as the result of gross carelessness and ignorance. Although numerous accidental ingestions by children and adults have been reported to the New York Poison Control Center, no known injury from these ingestions has been observed.

The threshold limit value for warfarin in air is 0.1 mg./M^3.

Signs and Symptoms of Poisoning in Man: The initial symptoms in an attempted suicide using warfarin were back pain and abdominal pain. The onset occurred one day after the sixth daily dose. A day after onset, vomiting and attacks of nose bleeding occurred. On the second day of illness, when admitted to the hospital, the patient was observed to have a generalized petechial rash. The prothrombin time was greatly prolonged. The coagulation time was definitely increased by the Lee-White method and slightly increased by the capillary tube method. Bleeding time was normal. Urine was normal in appearance but contained many red cells on microscopic examination.

In the Korean cases, the first symptoms appeared 7 to 10 days after the eating of warfarin was begun. Massive bruises or hematomata developed at the knee and elbow joints and on the buttocks in all cases. Extensive gum and nasal hemorrhage usually appeared about a day later and by the 15th day blood loss was extensive.

Animals intoxicated with the compound exhibit increasing pallor and weakness reflecting blood loss. Appetite and body weight are not specifically affected. The blood loss may be evident in the form of bloody sputum, bloody or tarry stools, petechiae, or externally visible hematomata. Hematoma formation is more common than free hemorrhage. If the hematoma is superficial, it will be marked by swelling and discoloration. However, in laboratory animals, hematomata are frequently so large in muscle septa that the entire upper or lower leg is grossly swollen, even though the lesion is so deep that no color is evident beneath the skin. There is no typical location for hematoma formation, the location of bleeding being apparently a matter of chance. Bleeding associated with the central nervous system may be of such location and extent as to cause paralysis of the hindquarters several days before death occurs.

Laboratory Findings: Of greatest specific significance is the markedly reduced prothrombin activity of the blood plasma as measured by the method of Quick or its modifications. More delicate tests may be made using both dilute and whole plasma. However, a clinical case should show marked increase of the prothrombin time of whole plasma.

A less specific test that will be abnormal in the presence of poisoning is the clotting time. The red count and hemoglobin gradually fall if bleeding continues. In terminal cases, a state of shock develops.

A chemical method for detecting the presence of warfarin is available but not practical for the hospital laboratory. Specimens of the stomach contents suspected of containing warfarin should be shipped refrigerated to the Toxicology Section for chemical analysis. See Appendix D.

Pathology: Animals killed by warfarin show most extreme pallor of the skin, muscles, and all the viscera. In addition, evidence of hemorrhage maybe found in any part of the body but usually only in one location in a single autopsy. Such blood as remains in the heart and vessels is grossly thin and forms a poor clot or no clot.

Treatment: After blood has been taken for prothrombin and other differential diagnostic tests, vitamin K in a dose of 65 mg. should be given three times on the first day of treatment irrespective of symptoms. Smaller doses should be continued until the prothrombin time has reached normal. In a seriously ill patient, a small transfusion of carefully matched whole blood should be given initially and repeated daily until the patient has returned to normal. Such a patient should be given vitamin K also. If it were ever necessary to treat a patient in shock from blood loss resulting from warfarin poisoning, frequent small transfusions and a complete consideration of the blood chemistry would be in order. Any large hematomata should be the subject of a surgical consultation, but any surgical action should be taken only after the clotting power of the blood is restored to normal.

The progress of the patient should be followed by the prothrombin test. Tests should be made at least twice daily until a return to normal is clearly established.

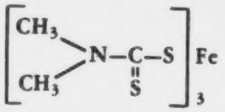
It will be noted that the suggested dosage of vitamin K is far in excess of the 1.0 mg. dose recommended in the Pharmacopoeia. It is, however, a safe dosage and is based on that already used successfully for some years in the treatment of excessive hypoprothrombinemia in the course of medication with coumarin drugs.

FUNGICIDES

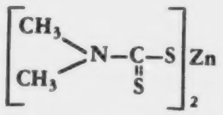
Dithiocarbamates

Identity: ferbam – ferric dimethyldithiocarbamate; ziram – zinc dimethyl dithiocarbamate; maneb – manganese ethylene bisdithiocarbamate; zineb – zinc ethylene bisdithiocarbamate; and nabam – disodium ethylene bisdithiocarbamate.

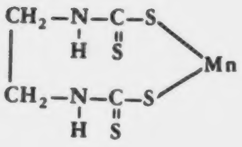
Chemical Formulae:



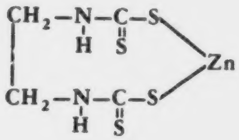
ferbam



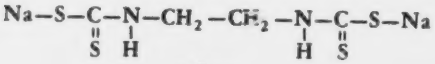
ziram



maneb



zineb



$$\mathrm{Na{-}S{-}\underset{\underset{S}{\|}}{C}{-}\underset{\underset{H}{|}}{N}{-}CH_2{-}CH_2{-}\underset{\underset{H}{|}}{N}{-}\underset{\underset{S}{\|}}{C}{-}S{-}Na}$$

nabam

Formulations: The several compounds are available as solutions up to 76%, as dusts up to 20%, and as wettable powders.

Uses: All the dithiocarbamates are fungicides used mostly on fruit crops and tobacco but also on vegetables and ornamentals.

Toxicology: The acute oral toxicity of dithiocarbamates to rats is as follows:

Compound	LD_{50}-Value (mg./kg.)
Ferbam	17,000
Ziram	1,400
Maneb	7,500
Zineb	> 5,200
Nabam	395

The exact dosage necessary to produce poisoning in man is not known for any of these compounds. Most applicators have considered the dithiocarbamates to be harmless and acted accordingly without experiencing anything more serious than mild dermatitis, pharyngitis, rhinitis, bronchitis, and conjunctivitis as a result of the rather heavy exposure. There is some evidence that much of the primary irritancy of formulations of these compounds may be due to the vehicle as well as to the active ingredients.

Organic mercury compounds

Identity: Mercury is bivalent in the organic compounds used as fungicides. As a rule, an alkyl (methyl, ethyl, methoxyethyl, etc.) or an aryl (phenyl, tolyl, etc.) mercury group is combined with an inorganic or organic acid or amide. Typical examples are: ethyl mercury phosphate, phenyl mercury acetate.

Most methyl mercury compounds appear to be more effective than other organic mercury compounds as fungicides. Some of the methyl compounds present a greater hazard to the user partly because of their higher volatility, although by simple LD_{50} tests the methyl mercury salts are not more toxic than the phenyl mercury salts.

Formulations: Both dusts and sprays are available. In some areas, there has been a trend to the use of sprays. Commercially treated seed generally are colored with a bright dye as a warning.

Users: The organic mercury compounds are used as seed dressings for the prevention of seed-borne diseases of grains, vegetables, cotton, peanuts, soybeans, sugar beets, and ornamentals. They may be used for the control of fungus diseases of turf, fruits, cereals, and vegetables but not under conditions that will leave any measurable residue in the food of man or animals. At least in other countries, organic mercury compounds have been used for the preservation of wood and in the paper, plastics, and fabric industries.

Routes of Absorption: These compounds are absorbed by the skin and by the respiratory and gastrointestinal tracts. Some of the alkyl compounds are highly volatile, thus increasing the hazard of inhalation.

Pharmacologic Action: Mercury, in whatever form, is a general protoplasmic poison. Differences in toxic manifestations of the organic mercury compounds and the better known inorganic compounds are seen particularly in chronic poisoning and are correlated with the greater storage of the organic compounds in the liver, kidneys, and brain. Storage in the brain may indicate a greater ability of some of the organic compounds to pass the blood-brain barrier but may represent only an equilibrium between blood and brain levels. At equivalent dosages of mercury, more is excreted in the urine after repeated feeding with phenylmercuric acetate than after similar feeding with mercuric acetate, but after injection more is excreted with the inorganic form. With repeated dosage, the organic compounds are more toxic. These facts have been offered as evidence of a greater initial absorption of the organic compounds (mercuric acetate vs. phenylmercuric acetate) from the gastrointestinal tract. Thus, the greater toxicity of the organic compounds, especially the alkyl ones is largely explained by their greater absorption and lesser excretion resulting in greater storage. Following daily oral dosage at the same rate, rats stored only traces of mercuric chloride or mercuric nitrate in the blood and brain; they stored more phenylmercuric acetate and much more cyano (methyl-mercuric) guanidine and methyl mercuric hydroxide in these tissues. A similar relationship was true for the liver and kidneys (inorganic < aryl < alkyl), but the concentrations were larger so that the storage of even inorganic mercury was easily detected. The concentration of all three classes in the different tissues increased in the order: brain < blood < liver < kidneys. Inorganic mercury is transported mainly in the plasma while both alkyl and aryl mercury are largely bound to the erythrocytes. The excretion of mercury in man exhibits two phases following cessation of exposure to ethyl mercury chloride, ethyl mercury phosphate or ethyl or phenyl mercury acetate. The first phase shows a slight rise in urinary mercury concentration, which reaches a peak that is variable in both magnitude and the interval of time after exposure ceases. Following the peak level, a second uniformly downward trend occurs.

All compounds of mercury can damage the kidney. Mercury vapor, its inorganic salts, and the lower alkyl compounds produce damage to the central nervous system. In the case of the methyl and ethyl mercury compounds, this damage can take the form of irreversible brain cell injury. Such changes may continue to progress for some time after the exposure to mercury has ceased.

Dangerous Single and Repeated Doses to Man: The exact amount of any organic mercury compound necessary to produce poisoning in man is not known but is obviously small. The acute oral LD_{50}-value for representative compounds in rats is approximately 30 mg./kg. The total dose of an organic mercury compound necessary to produce chronic poisoning in cats is about the same, that is 6 to 24 mg./kg. expressed as mercury. Acute poisoning by organic mercury has been reported infrequently in man, although such poisoning by methyl and other alkyl compounds has occurred. There have been many cases of chronic poisoning involving both inorganic and organic mercury. Most chronic cases caused by known organic chemicals were associated with repeated exposure in connection with the manufacture of alkyl compounds, their use for treating seed, or the eating of treated seed. Other cases were associated with the ingestion of seafood contaminated by industrial waste. The threshold limit value for organic mercury compounds in air is 0.01 mg./M^3.

Signs and Symptoms of Poisoning in Man: The acute symptoms associated with irritation of the gastrointestinal system and renal failure caused by inorganic mercury compounds are seldom observed in poisoning by organic mercury compounds and then almost exclusively in acute poisoning. Even the mild digestive disturbances and sore mouth seen in moderate, chronic, occupational poisoning by inorganic mercury are relatively rare. Instead, the nervous symptoms appear first, sometimes after relatively slight exposure and after months of latency. The patient may complain of headache; paresthesia of the tongue, lips, fingers, and toes; and other nonspecific dysfunction.

Early signs include fine tremors of the extended hands, loss of side vision, and slight loss of coordination, especially with the eyes closed as in the finger-to-nose-test. Incoordination is especilly notable in speech, writing, and gait. Incoordination may progress to the point of inability to stand or to carry out other voluntary movements. Occasionally there is muscle atrophy and flexure contractures. In other cases, there are generalized myoclonic movements.

There may be difficulty in understanding ordinary speech although hearing and the understanding of slow deliberate speech often remain unaffected. Irritability and bad temper are frequently present and may progress to mania. Occasionally the mental picture deteriorates to stupor or coma. Especially in children, mental retardation may be added to the symptoms of poisoning already mentioned.

Patients frequently become gradually much worse after their illness is recognized and exposure is stopped. Even in those cases in which recovery occurs in the course of months or years, there may be little or no real neurological improvement, only an adaptation and reeducation. The duration of illness in fatal cases has ranged from about a month to 15 years. Intercurrent infection, aspiration pneumonia, or inanition are the immediate causes of death.

The organic mercury compounds are strong irritants of the skin and may cause blisters or other dermatitis with or without associated systemic illness.

Laboratory Findings: The average excretion of mercury by normal people is 0.5 μg. daily in the urine and 10 μg. daily in the feces. Although there is some disagreement about the concentration of mercury that can be excreted safely, there is general agreement about the value of making the measurement. The most conservative view is that the concentration in the urine should not exceed 15 micrograms per liter (μg./1.) or slightly higher following exposure to alkyl mercury. Somewhat higher excretion can be tolerated following exposure to inorganic mercury, because any given level of excretion represents less absorption as compared with an organic compound. Other investigators, who have presumably used more sensitive chemical methods (although they failed to recognize the possibility of exposure to inorganic mercury in association with organic compounds), indicate that any operator exposed chiefly to alkyl compounds excreting more than 50 μg. of mercury per liter of urine should be placed on a "watch list" requiring weekly urinalysis and that any operator excreting more than 100 μg./1. should be removed from exposure. Hospitalized cases may excrete 600 or more micrograms per 24 hours (300 to 400 μg./1.).

Pathology: Extensive and relatively characteristic pathology has been reported in man and experimental animals. The most common findings are: (1) bilateral cortical atrophy around the anterior end of the calcarine tissue with disappearances of the striation of Gennari (associated with constriction of the visual fields) and (2) gross atrophy of the folia in the depths of the sulci of the lateral lobes and the declive of the cerebellum involving the granule cell layer (associated with ataxia). The hypothalamus, midbrain, and basal ganglia may be involved. The changes in the brain involve gliosis as well as the abnormality and loss of specific neurones. The bodies of the Purkinje cells are spared although the axones are affected. Changes in the peripheral nerve and the posterior columns have been reported in animals. Decrease in anterior horn cells with demyelination of the lateral columns of the spinal cord (associated with a case said to resemble amyotrophic sclerosis) has been reported; the difference may be related to the fact that a phenyl mercury compound was involved.

In fatal cases, the concentration of mercury in the organs has been in the following ranges: brain, 4.0 to 10.0 ppm; spinal cord, 3.5 to 40 ppm; liver, 14.0 to 20.0 ppm; kidney, 3.0 to 30.0 ppm; and lung, 2.0 to 4.0 ppm. More recent investigations have shown higher maximal values perhaps as a result of better analytical methods: brain, 21 ppm; liver, 71 ppm; kidney, 144 ppm. Excessive mercury may be found in the hair also. Comparable values obtained by modern techniques do not seem to be available in connection with chronic poisoning by inorganic mercury.

Differential Diagnosis: Viral encephalitis, poisoning by certain other metals, and some neurological disorders of unknown or hereditary cause must be considered. Diagnosis depends on a history of exposure and the measurement of mercury in urine and tissues.

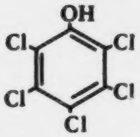
Treatment: In poisoning by alkyl mercury compounds, BAL is considered of doubtful value or even harmful. It may be useful in treating sequelae of alkyl mercury poisoning perhaps because inorganic mercury may be left in the tissues. EDTA has also been used as an antidote but its value is not established.

Prevention of Poisoning: If mercury compounds must be used instead of less poisonous fungicides, then the use of masks, rubber gloves, and separate work clothing is necessary. More elaborate protective devices are recommended under manufacturing conditions. Special closed machinery is available for applying dressing to seed and should be used if possible. Even if the best equipment is available, all clothing, including shoes, must be changed after work. Smoking, chewing gum or tobacco, drinking, or eating are prohibited during work. Tobacco, gum, or candy must not be carried in work clothing. Scrupulous personal hygiene is required. Workers should receive preemployment medical examination to exclude those with neurasthenia, nervous disease, dermatitis, liver disorder, hypertension, or defective kidney function. Persons with repeated exposure should have periodical medical examination and frequent, regular analysis of the urine for mercury.

Pentachlorophenol

Chemical Name: pentachlorophenol

Chemical Formula:



Formulations: Pentachlorophenol, a crystalline solid, is soluble in various organic solvents, including the petroleum oils in which it is applied. It is frequently used as the sodium salt, which is freely soluble in water.

Uses: Pentachlorophenol is an insecticide, moluscicide, herbicide, fungicide, and bactericide. It is used to control termites and other wood insects and various snails, including those that carry schistosomiasis. It is used as a weed killer, cotton defoliant, and preservative for timber.

Routes of Absorption: Pentachlorophenol is absorbed by the skin as well as after inhalation or ingestion.

Pharmacologic Action: The action of pentachlorophenol is similar to that of the dinitrophenols (which see) and consists of an increase in the metabolic rate leading to a marked increase in body temperature, collapse, and death. The main action of the chemical is a rapid uncoupling of oxidation and phosphorylation cycles. Although illness may be produced by the cumulative action of several doses, the onset of critical illness tends to be sudden and the course of the disease rapid. In 19 cases for which the information is available, the time from first symptoms to death ranged from 3 to 30 hours and averaged 14 hours.

Excretion occurs largely in the urine. In certain fatal cases, it seemed that the victim was unusually susceptible by virtue of renal deficiency. This hypothesis was supported by experiments which showed that rabbits made nephritic experimentally were very much more easily poisoned by pentachlorophenol than were normal animals.

Dangerous Single and Repeated Doses to Man: The exact dosage necessary to produce illness is not known. It is clear that the largest dosage that produces no illness whatever is little less than the fatal dosage. It is claimed that one man drank a glassful of 2% solution of the sodium salt with no effect except a hangover. One man died after working 6 days as a mixer preparing 2.1% cotton defoliant from 40% concentrate. Nine died after dipping timber by hand and without any protection in 1.5% to 2% solution for periods varying from 3 to 30 days with an average of 13 days; this is typical of several other situations in which accidents have occurred. The threshold limit value for pentachlorophenol in air is 0.5 mg./M^3.

Signs and Symptoms of Poisoning in Man: Nonfatal systemic poisoning is characterized by weakness, by more or less marked loss of appetite and weight, sometimes by a feeling of constriction in the chest and dyspnea on moderate exercise, and almost always by excessive sweating. Headache, dizziness, nausea, and vomiting may be present.

In fatal cases the temperature is frequently extremely high [up to 108°F (42.2°C)], but may be only moderately elevated. Sweating, dehydration, and dyspnea are present and there may be pain in the chest or abdomen. The pulse is rapid. Coma appears early. There is frequently a terminal spasm.

Under some conditions of use, pentachlorophenol causes irritation of the skin, conjunctiva, and upper respiratory tract even at dosages that do not produce systemic disease. Dermatitis may be acneform or eczematous.

Pathology and Laboratory Findings: The pathology is not characteristic except that the high temperature of the body may be noted if autopsy is performed within a few hours after death. The organs frequently show some congestion and there may be some cerebral edema. Degenerative changes in the liver and kidneys have been observed in a few cases. In one case of fatal occupational poisoning, with autopsy three days after death, pentachlorophenol was found in the following concentrations: lung, 76 ppm; blood from lung, 97 ppm; liver, 62 ppm; blood from liver, 46 ppm; and kidney, 84 ppm. A child who ingested the material showed the following concentrations: liver, 59 ppm; blood from liver, 53 ppm; kidney, 41 ppm; and urine (post mortem), 28 ppm.

Nonfatal cases have shown 3 to 10 ppm of pentachlorophenol in the urine and sometimes traces of albumin. Concentrations were 55 and 96 ppm in urine taken at autopsy from adults. Early reports of concentrations as low as 7 ppm in fatal cases may be in error.

Differential Diagnosis: The greatest danger is that poisoning by pentachlorophenol will be mistaken for poisoning by an organic phosphorus insecticide, which is also characterized by sweating, difficulty in breathing, and pain in the chest and abdomen.

Treatment: The use of atropine sulfate is absolutely contraindicated. Treatment is symptomatic and difficult. An effort must be made to maintain the fluid and electrolyte balance and to keep the body temperature within tolerable limits.

Prevention: The first rule of prevention is good general hygiene with emphasis on protection of the skin of workers. At least under field conditions, it is wise to alternate workers so that repeated exposure is for a maximum of two weeks. During the preemployment examination, careful measurement of renal function should be made in order to exclude applicants with deficient function.

HERBICIDES

Arsenic

Identity and Formulae: Elementary arsenic forms two oxides: the trioxide, As_2O_3, and the pentoxide, As_2O_5. Arsenic trioxide (trivalent) reacts with water to form arsenous acid, H_3AsO_3, which is known only in solution and forms three series of salts: orthoarsenites (e.g., Na_3AsO_3), metaarsenites (e.g., $NaAsO_2$), and pyroarsenites (e.g., $Na_4As_2O_5$). Arsenic pentoxide (pentavalent) reacts with water to form three acids that may be isolated: orthoarsenic acid, H_3AsO_4; metaarsenic acid, $HAsO_3$; and pyroarsenic acid, $H_4As_2O_7$. These acids form the corresponding salts: orthoarsenates, metaarsenates, and pyroarsenates. A few organic arsenic compounds are also used as pesticides.

Although a great many arsenicals have had some use, the following are of most importance:

Name	**Synonym**	**Formula**
Arsenic trioxide	white arsenic	As_2O_3
Sodium arsenite		Mixture, see above
Paris green	copper aceto-meta-arsenite	$Cu(CH_3COO)_2 \cdot 3Cu(AsO_2)_2$
Lead arsenate	acid lead arsenate standard lead arsenate dilead arsenate	$PbHAsO_4$
Basic lead arsenate	lead hydroxy-arsenate	$Pb_4(PbOH)(AsO_4)_3 \cdot H_2O$
Calcium arsenate		a complex mixture
Dimethylarsinic acid	Arsan cacodylic acid	$(CH_3)_2AsO(OH)$
Disodium methyl arsenate		$Na_2CH_3AsO_3 \cdot 6H_2O$

Formulations and Uses: Arsenic trioxide in the form of a powder is used as a rodenticide. Arsenites are more soluble and more rapidly toxic than corresponding arsenates; therefore, arsenites are used as rodenticides and herbicides, and in insecticidal baits. Sodium arsenite is usually sold as a solution. Dimethylarsinic acid and disodium methyl arsenate are herbicides. In some countries sodium arsenite was used to dry up potato tops in preparation for mechanical harvesting, but the practice is very dangerous. Paris green, although an arsenite, may be applied to foliage but the arsenates are less phytotoxic and, therefore, preferred. Lead arsenate is usually used as a wettable powder, calcium arsenate as a dust. Paris green impregnated on vermiculite is used to an increasing degree as a mosquito larvicide. The use of arsenical insecticides in agriculture has decreased greatly since the introduction of DDT and later poisons, but the use of arsenical herbicides has increased.

Route of Absorption: Arsenic is absorbed chiefly by the respiratory and gastrointestinal tracts. However, some is absorbed by the intact skin, and systemic illness may follow application of arsenical ointment to eczematous skin.

Pharmacologic Action: Arsenic in whatever form is a general protoplasmic poison. It binds organic sulfhydryl groups, thus inhibiting a number of enzymes, notably pryuvate oxidase and the phosphatases, so that tissue respiration is reduced. The chief pharmacodynamic action is dilatation and increased permeability of the capillaries. This action is strongest in the intestines regardless of route of absorption. Arsine (hydrogen arsenite), is a powerful hemolytic agent but it is unlikely to be found in connection with pesticides. Most commercial arsenic formulations are irritant, at least in part because of their impurities. Pure compounds are only weakly irritant but they slowly kill cells on prolonged contact, and by local action on capillaries they cause congestion, stasis, thrombosis, ischemia and necrosis. Such necrosis extends into the bone in some instances. It is generally stated that arsenic can cause cancer, especially of the skin, but the epidemiology is not clear. No cases have been clearly traced to occupational or accidental contact with pesticides.

Dangerous Single and Repeated Doses to Man: A dose of 5 to 50 mg. of arsenic trioxide is toxic. A dosage of 128 mg. has proved fatal but recovery has occurred after much larger doses. The effectiveness of arsenical rat poisons varies greatly with the grind of the powder; very fine powders approach the toxicity of solutions containing an equivalent amount of arsenic. Thus the ease of absorption influences the toxicity to a marked degree. The repeated dose necessary to produce poisoning is less well known. The "therapeutic" dose of arsenic trioxide (1 to 2 mg. three times daily) that used to be employed as a tonic frequently led to mild poisoning. The threshold limit for arsenic is 0.5 mg./M^3, a value higher than that for lead because arsenic is more efficiently excreted.

Signs and Symptoms of Poisoning in Man: For many years, arsenic has been the most important single cause of accidental deaths associated with pesticides. In 1956, it caused 35% of such cases. Accidental poisoning by arsenic pesticides is almost always acute and often involves children (74% of these cases in 1956 involved children 5 years old or younger). Abdominal pain and vomiting often start within an hour of ingestion, although the onset may be delayed particularly if foul play is involved and the dosage is controlled. Death may result from a severe fall in blood pressure and collapse as in "dry" cholera. Generally death is delayed for 1.5 to 3 days after onset and sometimes as much as 14 days. In this event, death follows vomiting and profuse, painful diarrhea; the clinical picture is similar to cholera because of the character of the stools and the great dehydration of the patient. If the patient survives the acute phase, exfoliative dermatitis or neuritis may appear. People with this polyneuritis have pain, burning, and tenderness of the affected limbs and trouble in walking. Chronic poisoning has not been a significant problem in pesticide applicators; cases reported in vineyard workers in Germany may have involved the drinking of contaminated wine. Chronic poisoning is well known from other sources. It usually involves the frequently insidious onset of loss of appetite, weight loss, weakness, nausea, alternating diarrhea and constipation, colic, peripheral neuritis, dermatitis, some loss of hair, giddiness, and headache. Cyanosis of the face may be present. The dermatitis may be erythematous, pustular, or even ulcerative. Burning and itching may be present and there may be serous discharge. With most arsenic compounds, the skin lesions tend to be most marked in the area of greatest contact. They are considered mainly the result of direct toxic action. The action may involve the face, eyelids, conjunctivae, or even cornea. There may be irritation of the nose, pharynx, and trachea. Perforation of the nasal septum has occurred. In less acute cases, hyperkeratosis, hyperhidrosis, or melanosis may occur. White transverse bands in the nails frequently accompany polyneuritis. The bands gradually migrate to the free edge of the nails as the result of growth of the nails. A highly characteristic dermatitis confined to the scrotum, inguinal area, and nasolabial folds may follow moderate occupational exposure to Paris green. The lesions begin with erythema, frequently become eczematous and weeping, and may start to heal with the formation of a black scab. A sensitization reaction may be involved because the distribution does not correspond to the distribution of insecticide on the skin, and the dermatitis generally occurs in the absence of typical poisoning.

Laboratory Findings: Normal people may excrete arsenic in the urine at rates as high as 0.17 ppm (as As_2O_3). Blood levels as high as 1 ppm have been reported in normal people as the result of arsenic in ordinary food and water. Concentrations in other soft tissues may be as high as 7.6 ppm; the hair may have 10 to 15 ppm. Asymptomatic chemical workers may show arsenic at a concentration of 100 ppm in the hair and 0.82 ppm or more in the urine. Serious but nonfatal cases showed urinary excretion as high as 6.2 mg. per 24 hours or between 4 and 6 ppm. Victims of acute poisoning showed 148 and 150 ppm of arsenic in the liver. Values from the kidneys in fatal cases have ranged from 9.2 to 91 ppm.

Electrocardiographic changes may be present. In arsine poisoning (unlikely in connection with pesticides), severe anemia is found in the presence of a normal bone marrow; the urine shows hemoglobin and sometimes albumin.

Autopsy Findings: In acute poisoning, erosion and inflammation of the stomach and upper intestinal tract may be marked. The liver may show degenerative lesions and in chronic poisoning these can lead to cirrhosis. Unless death is very rapid, the severe dehydration produced by acute poisoning gives the body an emaciated appearance even though a normal amount of fat remains. The alimentary canal shows a large amount of fluid, shreds of mucous, and false membrane in the absence of marked corrosion – a picture similar to that in cholera. The body may decay more slowly than would be expected in the same amount of time at the same temperature.

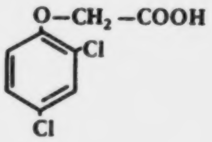
Treatment: If ingestion is suspected, the stomach should be emptied by vomiting and lavage with warm water followed by a saline cathartic. BAL (Dimercaprol) is a specific antidote; it should be given intramuscularly at the rate of 3 mg./kg. every four hours for the first two days, every six hours on the third day, and twice daily thereafter until recovery is complete. The drug is available as a 10% solution in peanut oil with 20% benzyl alcohol. Dehydration should be combatted with saline infusions guided, where possible, by laboratory studies. The diet should be liquid. BAL is indicated in the various forms of chronic poisoning as well as in acute poisoning.

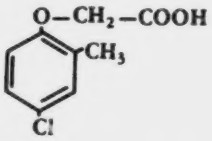
Prevention: Most accidental cases of poisoning by arsenical pesticides would be prevented if formulations were always kept in the original, labeled containers and the containers were stored so that they were absolutely inaccessible to children.

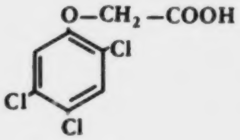
Chlorophenoxy herbicides

Identity: 2,4-D – 2,4-dichlorophenoxyacetic acid
2,4,5-T – 2,4,5-trichlorophenoxyacetic acid
MCPA – 2-methyl-4-chlorophenoxyacetic acid

Chemical Formulae:


2,4-D


MCPA


2,4,5-T

Formulations: The acids themselves are sometimes used but the salts or esters are more widely applied as weed killers. The alkyl amine salts of 2,4-dichlorophenoxyacetic acid (e.g., triethylamine, triethanolamine) have largely replaced the inorganic salts (sodium or ammonium) as herbicides. A wide range of simple alkyl esters (e.g., isopropyl and butyl) are used when relatively high volatility is desired; other esters (e.g., butoxyethanol, tetrahydrofurfuryl) are used when low volatility is required. A similar array of derivatives of 2,4,5-T and of MCPA are available. Other related hormone-type herbicides include 3,4-D,*p*-chlorophenoxyacetic acid, various phenoxyproprionic acids and various phenoxybutyric acids. In general, each of these may be prepared as the acid, inorganic salts, amine salts, or esters. These compounds are sold as dry salts, pastes, emulsifiable concentrates, water-wettable powders, and dusts varying in strength of active ingredients from 2% to 98%. A wide variety of solvents have been used with them including kerosene, Stoddard's solvent, xylene, and methylated naphthalenes. The active ingredients are applied at final dilutions as low as 3 ppm and as high as 25% (250,000 ppm) depending on the use.

Uses: As herbicides, 2,4-D-type compounds are used for selective weed control in many crops on over 50 million acres. These compounds are used widely as eradicative herbicides in industrial weed control. They are also used in very high dilutions as hormone sprays to prevent the early dropping of fruit.

Routes of Absorption: These compounds may be absorbed if taken by mouth or presumably if inhaled. Skin absorption is slight.

Pharmacologic Action: 2,4-D and related compounds act as growth hormones in plants. They have no hormonal action in animals, but the mechanism of their toxic action is poorly understood.

Dangerous Single and Repeated Doses to Man: The acute oral toxicity of representative compounds to the rat is as follows:

Compound		LD_{50}-Value (mg./kg.)
2,4-D	– acid	375
	– sodium salt	666 – 805
	– mixed butyl esters	620
	– isopropyl ester	700
2,4,5-T	– acid	500
	– mixed butyl esters	481
	– isopropyl ester	495
MCPA	– acid	700
	– amine salt	1,200

The oral dose required to produce symptoms in man is probably 3 to 4 g. One man consumed 500 mg. of purified 2,4-D per day for 21 days without ill effect. When 2,4-D acid was investigated as a possible treatment for disseminated coccidiodomycosis, the patient had no side effects from 18 intravenous doses during 33 days; each of the last 12 doses in this series was 800 mg. or more; the last being 2,000 mg. (about 37 mg./kg.). A nineteenth and final dose of 3,600 mg. produced acute illness described below. An oral dose of not less than 6,500 mg. led to death in a case of suicide.

Animals fed 2,4-D or 2,4,5-T tolerate for months daily doses only slightly smaller than those which cause toxic effects when given only once. Thus, cumulative effect is minimal. Recovery from poisoning is complete.

The threshold limit value for 2,4-D in air is 10 mg./M^3, and the tentative value for 2,4,5-T is the same.

Signs and Symptoms of Poisoning in Man: The patient given 3,600 mg. of 2,4-D acid intravenously suffered coma, fibrillary twitching of some muscles, hyporeflexia, and urinary incontinence. Seven hours after infusion the patient could be roused but lapsed back into deep sleep. Twenty-four hours after dosage he was eating well but still complained of profound muscular weakness; within an additional 24 hours he had apparently recovered from all effects of the plant hormone. In what was presumably attempted suicide, ingestion of an unknown amount of 2,4-D resulted in "prolonged stupor" followed by recovery. The body of the man who committed suicide showed signs of convulsions prior to death.

Animals killed quickly by large doses of 2,4-D are thought to die of ventricular fibrillation. If death is delayed, myotonia, stiffness of the extremities, ataxia, paralysis, and coma are seen. Repeated doses that may or may not eventually lead to death produce loss of appetite, loss of weight, vomiting, depression, roughness of coat, and general tenseness and muscular weakness. It may be significant that the myotonia characteristic of poisoning by 2,4-D in animals has not been reported in man.

Three cases of "peripheral neuritis" among men very recently exposed to 2,4-D were seen at one clinic in a single month. No valid toxicological or epidemiological evidence was given to support a causal relationship. Although more than 700,000,000 pounds of 2,4-D and related compounds have been manufactured and used, no similar cases have been reported.

As with other chemicals, 2,4-D may be a cause of contact dermatitis, but this effect in man is neither so common nor so severe as animal experiments would suggest.

Laboratory Findings: Animal studies have not indicated any useful laboratory tests.

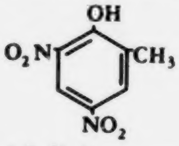
Pathology: Experimental animals killed by 2,4-D show irritation of the stomach (or the abomasum of ruminants), minor liver and kidney injury, and sometimes congestion of the lungs. Nonspecific hyperemia of the lungs, liver, and brain were found in the case of suicide.

Differential Diagnosis: The occurrence of myotonia soon after heavy exposure to 2,4-D would be suggestive of poisoning. 2,4,5-T produces only mild spasticity but may produce difficulty in swallowing. In the absence of myotonia, poisoning by solvents and the possibility of neurological disease unrelated to chemicals must be considered in view of the low toxicity and good safety record of the hormone-type herbicides.

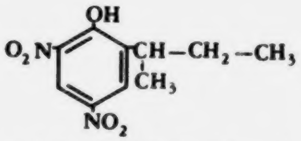
Treatment: If poisoning were to occur, for example in attempted suicide, treatment would be symptomatic.

Dinitrophenols

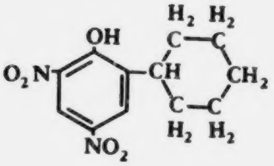
Identity: A number of substituted dinitrophenols, alone or as salts of aliphatic amines (triethanolamine or isopropanolamine) or alkalies (sodium or ammonium hydroxide), are sold under many trade names, frequently with a suffix to indicate the formulation. Representative materials are as follows:



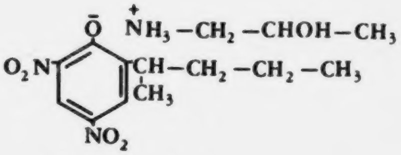
4,6-dinitro-o-cresol (DNOC)
(2-methyl-4,6-dinitrophenol)



2-*sec*-butyl-4,6-dinitrophenol



2-cyclohexyl-4,6-dinitrophenol



isopropanolamine salt of 2-*sec*-amyl-4,6-dinitrophenol

Formulations: Dinitrophenols are marketed as 1.5% to 2.5% solutions in oil and up to 53% water-wettable powders. They are also available in the form of 20% salts in 14% oxidized oil. Frequently 2% sodium chromate is included in liquid concentrates as a corrosion inhibitor.

Uses: The substituted dinitrophenols are used, in different formulations, as fungicides, insecticides, miticides, or herbicides. They are used extensively in dormant sprays for the control of mites, aphids, scale insects, and other pests in overwintering stages. They are useful as acaricides in greenhouse, field, and orchard. In other countries, DNOC has been released by aircraft against airborne swarms of grasshoppers. The compounds may be used as eradicant herbicides in such locations as roadsides and right-of-ways, or as selective weed killers in fields or pastures, or as blossom thinners for tree fruits.

Routes of Absorption: All of the compounds listed may be absorbed in toxic amounts by inhalation or ingestion. DNOC and the secondary butyl derivative may be absorbed through the skin to a dangerous degree while the cyclohexyl derivative is not absorbed to an appreciable extent by this route.

Pharmacologic Action: All of the compounds increase the oxidative metabolism and therefore the heat production of the body chiefly by direct peripheral action.

Dangerous Single and Repeated Doses to Man: The dangerous single dose of DNOC has been estimated to be 2 g. (about 29 mg. kg.). No toxic effects were noted by any of five volunteers after the ingestion of the first of 5 or more doses of 75 mg. of DNOC leading to blood levels of 10 ppm or slightly less. Two volunteers who ingested doses of 75 mg. of DNOC per day for 5 and 7 days, respectively, experienced lassitude, headache, and malaise.

Because DNOC is a cumulative poison and is excreted very slowly by human beings, persons who have suffered any symptoms of poisoning should be removed from risk of further absorption for a period of at least 6 weeks. Less is known of the toxicity of the other compounds to man but their toxicity to the rat is similar, as shown in the table below.

The threshold limit value for DNOC in air has been set at 0.2 mg./M^3.

ORAL TOXICITY OF SELECTED SUBSTITUTED DINITROPHENOLS TO THE RAT

Compound (R = 4,6-dinitrophenol)	Tolerated Acute Dosage (mg./kg.)	Acute LD_{50} (mg./kg.)	Tolerated Concentration in Diet (ppm)
2-Methyl-R (DNOC)	10	30	100
2-*sec*-Butyl-R	5	37	100
2-Cyclohexyl-R	30	80	500

Signs and Symptoms of Poisoning in Man: The signs and symptoms of confirmed acute DNOC poisoning in man have closely paralleled those of experimental animals and include nausea, gastric distress, restlessness, sensation of heat, flushed skin, sweating, deep and rapid respiration, tachycardia, fever, cyanosis, collapse, and coma. Acute poisoning with DNOC usually runs a rapid course; death or almost complete recovery within 24 to 48 hours is the general rule.

The increase in metabolic rate is proportional to the dose of the toxicant absorbed, and very high levels (up to 4 times normal) may be reached temporarily. However, with high metabolic rates, heat production so exceeds the physiologic capabilities of heat dissipation that fatal hyperthermia may result. DNOC is much more effective in raising the body temperature if the temperature of the surroundings is 22°C. (72°F.) or over. If the external temperature is 16°C. (61°F.) or below, increased oxidation and pyrexia are not produced. On the contrary, in this situation, DNOC lowers oxidation by greatly diminishing or abolishing shivering, and eventually causes rapid cooling of the animals. Heat regulation is, therefore, disturbed in both directions, so as to exaggerate the detrimental effects of external temperature.

The signs and symptoms of chronic DNOC intoxication may include fatigue, restlessness, anxiety, excessive sweating, unusual thirst, and loss of weight. Yellow staining of the conjunctivae may be noted though staining of skin is not necessarily indicative of poisoning. Cataract formation is another possible sequela of chronic DNOC poisoning.

Laboratory Findings: The most striking laboratory finding is the increased basal metabolic rate (BMR). A test is available for determining the blood and urinary content of DNOC. Repeated daily oral doses of 75 mg. gives rise, after 3 days, to a blood level of about 20 ppm. Symptoms appear when the concentration in the blood reaches 40 ppm, or more. A case with a blood level of 70 ppm, terminated fatally. In very cool weather, blood levels as high as 50 ppm may be tolerated without symptoms.

Pathology: In persons who have died from the effect of DNOC, yellow staining of the organs, tissues, and fluids due to the presence of the sodium salt of DNOC may be noted. The lungs are congested and there is usually some edema and a few petechial hemorrhages. There may be similar hemorrhagic changes in the brain and gastric mucosa.

Differential Diagnosis: The symptoms of chronic poisoning from substituted dinitrophenols resemble those of hyperthyroidism rather closely. BMR determination, of course, is of no value in differentiating between these two conditions. An exposure history should provide some basis for making a distinction. In doubtful cases, this may be supplemented by urine and blood determinations for DNOC content, and by the use of other tests for thyroid function such as blood protein-bound iodine, and rate of uptake of radioactive iodine by the thyroid gland.

Acute poisoning is so rapid in onset that it will not be confused with hyperthyroidism. It may be confused with other forms of poisoning merely because of rapidity and severity. Confusion with poisoning by an organic phosphorous compound would be disastrous.

Treatment: Atropine sulfate is absolutely contraindicated. The poison should be promptly removed from the skin and/or gastrointestinal tract with an appropriate alkaline agent. No attempt beyond ordinary washing should be made to remove the deeply-penetrated, persistent stain from the skin or hair.

Treatment consists of an ice bath to reduce the patient's fever, the administration of oxygen to assure maximal oxygenation of the blood, and the infusion of large quantities of isotonic saline to replace the fluid and electrolyte lost by sweating.

It has been claimed that the intravenous injection of 10 ml. of a 2.5% solution of sodium methyl thiouracil rapidly reduces the BMR in persons in whom the rate of metabolism has been increased by DNOC.

Prevention: Applicators should observe all necessary precautions in using dinitrophenols and should have routine periodic checks of blood levels. The significance of different concentrations of DNOC in whole blood is as follows:

0 - 10 ppm	trivial
11 - 20	appreciable absorption
21 - 30	unsafe
31 - 40	likely to cause some toxicity
41 - 50	dangerous
> 50	critically dangerous

Corresponding values for plasma or serum are approximately twice as high.

SOLVENTS

Introduction: Solvents and other carriers may contribute to the danger of insecticidal formulations either through their inherent toxicity or through their solubilizing action on the so-called active ingredients. In some instances, cases of poisoning by solutions of insecticides have been characterized by symptoms and clinical course indistinguishable from those caused by the solvent alone. On the other hand, a clinical course characteristic of the active ingredient has been present in other cases.

Kerosene

Identity: Kerosene, or coal oil, is a mixture of principally aliphatic hydrocarbons distilled from petroleum in the temperature range of 204° to 315°C. The empirical formula is C_nH_{2n+2} (Where n ranges from approximately 10 to 16). Other petroleum fractions such as diesel fuels Nos. 1 and 2 are closely related chemically, and much of this section pertains to such fractions also.

Formulations: Kerosene is one of the most common solvents in insecticidal solutions and emulsions, especially in sprays of the household type, which may contain up to 98% kerosene. This solvent is usually highly refined and – unlike fuel grade kerosene – essentially odorless. Other toxic solvents are often included in formulations of insecticides.

Uses: Kerosene is used as a solvent, diluent, and vehicle in sprays for household, agricultural, and public health use. Kerosene is also commonly used alone as an herbicide, as a fuel, as an industrial solvent, and for many other purposes.

Routes of Absorption: Kerosene may be absorbed orally or through the respiratory tract. Its dermal absorption is not significant for systemic poisoning under ordinary conditions of exposure

Pharmacologic Action: Systemically, kerosene acts as a narcotic producing depression that may or may not be preceded by an excitement phase. At least in connection with ingestion, depression *per se* is apparently never fatal although it may be alarming. Liver and kidney damage may occur in severe cases. Coma and other major central nervous system effects are frequently present in cases that result from fumes and are serious enough to come to medical attention. However, such serious effects are reported in only 3% to 6% of cases involving ingestion. In one series of 204 cases, 4% of the children were semiconscious but none had convulsions, 40% were lethargic and 28% had gastrointestinal symptoms; however, **all** had respiratory symptoms and 3% died. Ingestion of kerosene has been known to produce rapid death by gross aspiration and occlusion of the respiratory system. Even when death does not occur promptly, there is abundant evidence that the pneumonia commonly seen in children who swallow kerosene usually results from aspiration. The aspiration usually occurs at the moment of ingestion or as the result of vomiting within the first hour. The ratio of the oral to the intratracheal LD_{50} for kerosene is approximately 140:1. Animal experiments prove that kerosene is absorbed from the gastrointestinal tract. Concentrations of aromatics as high as 140 ppm and of aliphatics as high as 917 ppm were found in blood or tissues. In spite of this absorption, the lungs of animals receiving dosages of 13 ml./kg. or less with precautions to prevent aspiration were normal histologically when the animals were sacrificed. The lungs of rats dosed at 18 ml./kg. showed moderate changes on sacrifice, and rats killed by 30 to 40 ml./kg. showed more marked pathology of the lungs as well as liver and kidney changes. Fatal aspiration leads to gross hemorrhagic pneumonitis most severe in the hilar and dependent portion of the lung in contrast to the even distribution of hemorrhage following rapid intravenous injection or pulmonary edema following slow intravenous injection. It would appear that, in the absence of aspiration, the dosage of kerosene necessary to produce pneumonitis or other serious effects is greater than that likely to be ingested. Evidence on the effect of mineral oil and vegetable oil on absorption of kerosene is conflicting.

Like many other oils, kerosene is a local irritant and may cause a maculopapular eruption of the exposed skin. The irritation tends to increase and later decrease with repeated exposure over a long period.

Dangerous Single Dose to Man: Although kerosene is a common cause of poisoning especially in children, the amount taken is seldom known. Survival has been reported following the ingestion of one liter, but death has followed the ingestion of doses as small as 30 ml., especially after kerosene was aspirated. The air concentration capable of producing acute symptoms by inhalation is not known.

Dangerous Repeated Dose to Man: Chronic intoxication has not been reported.

Signs and Symptoms of Poisoning of Man: The use of kerosene sprays in closed or poorly ventilated spaces may lead to fullness of the head, headache, blurred vision, dizziness, unsteady gait, and nausea. More massive exposure may cause collapse, nervous twitching; and coma before the victim is apparently aware of overexposure and before he seeks fresh air.

Ingestion frequently results in immediate gagging and coughing and thus leads to aspiration of the oil. The initial symptoms are followed by deep drowsiness. In the more serious cases, bronchopneumonia may develop in 24 to 36 hours. Chest signs are likely to be few or absent even when X-ray of the chest reveals an extensive bronchopneumonia. Liver and kidney damage may be manifest by hepatomegaly and by albumin, cells, and casts in the urine.

Laboratory Findings: Leukocytosis and albuminuria or casts (generally in severe cases, only) may be present. It may be possible to recognize kerosene in stomach contents by its characteristic odor. This odor will be negligible or absent in poisoning by deodorized kerosene. X-ray and liver and kidney function tests should be used to follow the progress of visceral damage.

Pathology: Bronchopneumonia, visceral congestion, acute pulmonary edema, and hemorrhage. Evidence of inflammation of the upper gastrointestinal tract may be seen in cases that die early.

Differential Diagnosis: The case history will usually establish the diagnosis. The characteristic odor may or may not be present. Where there is doubt, poisoning by alcohol and other solvents and by a wide range of narcotic agents may be considered as well as diabetic coma.

Treatment: The injury caused by inhalation of kerosene fumes seldom requires any treatment except prompt removal from exposure.

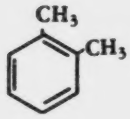
If kerosene containing no insecticide has been ingested, gastric lavage may be done mainly as a precaution against regurgitation and aspiration from the gastrointestinal tract. A recent study has shown that gastric lavage was not harmful to patients but there was no conclusive evidence that it was beneficial. This is encouraging in connection with cases in which the ingested kerosene was the solvent for an insecticide that should be removed rapidly and thoroughly. If attempted, the gastric lavage should be done very early before narcosis sets in and every other possible precaution, including use of an intratracheal tube with inflated balloon, should be taken so that the lavage itself does not lead to aspiration of the kerosene. Emetics are contraindicated. Oil laxatives should be avoided, especially if the kerosene was the vehicle for an insecticide. A saline laxative may be helpful. Sedatives and stimulants may be used symptomatically in moderation. Antibiotic therapy does not benefit kerosene pneumonia as such, but it may be of some benefit in preventing bacterial invasion. Oxygen should be used promptly if the patient shows any respiratory difficulty or the slightest cyanosis. Cortisone and related drugs have been used for treating chemical pneumonitis caused by kerosene and other oils, but the value of this treatment remains to be determined. There seems to be no doubt that the inflammatory reaction is suppressed and symptoms are relieved, but there is some indication that this merely postpones the removal of oil from the lung and healing of the injury. Thus, the value of adrenocortical steroids for the treatment of kerosene pneumonitis can be decided only after further carefully-controlled study. Liver damage may be minimized by the use of a diet low in fat and adequate in carbohydrate. The usefulness of lipotrophic drugs has not been investigated in this connection. Kidney involvement is rarely sufficient to merit special treatment and for those rare cases where the kidneys are seriously involved the treatment should be the same as for toxic nephritis of other etiology.

Kerosene dermatitis requires no special treatment and will regress spontaneously if exposure is discontinued. Cleanliness will help to prevent its occurrence.

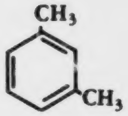
Xylene

Chemical Name: A mixture of *o*–, *m*–, and *p*-xylene. (The ortho isomer is predominant in percentage.)

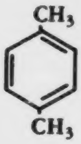
Chemical Formulae:



ortho
isomer



meta
isomer



para
isomer

Formulations and Uses: Xylene is a common solvent in insecticidal solutions, emulsifiable concentrates, and emulsions. It is extensively used in industry especially as the main constituent of "solvent naphtha."

Routes of Absorption: Xylene is absorbed when taken orally or inhaled by the respiratory tract. Its dermal absorption is not significant under ordinary conditions of exposure.

Pharmacologic Action: Undiluted xylene is a severe irritant to mucous membranes and delicate skin. Xylene can cause a local dermatitis on any type of skin if used repeatedly. When absorbed, it acts as a narcotic and affects the circulating red blood cells.

Dangerous Single and Repeated Doses to Man: The smallest oral dose which may prove fatal is unknown. The threshold limit value for xylene in air has been set at 870 mg./M^3.

Signs and Symptoms of Poisoning in Man: Local application to tender skin or to the eyes results in intense burning. Exposure to vapors in a poorly ventilated room results in headache, disturbed vision, dizziness, poor coordination, and nausea. Severe exposure may lead to collapse and coma. Repeated exposure may lead to moderate anemia as well as headache, dizziness, malaise, loss of appetite, ready fatigue and later nausea, chilliness, and hemorrhage from the nasal mucosae. It should be pointed out that commercial grades of xylene may be contaminated by appreciable amounts of benzene, so that the inhalation of the vapor may affect the hematopoietic system.

Laboratory Findings: Complete blood studies including, if necessary, sternal puncture should be done if chronic xylene poisoning is suspected. Macrocytosis, moderate decrease of the red cells, and lymphocytosis are suggestive but not diagnostic.

Differential Diagnosis: Diagnosis is usually established by the history. If in doubt, alcohol and a wide variety of narcotic agents must be considered. Changes in the blood picture must be distinguished from similar changes caused by other materials and from acute leukemia.

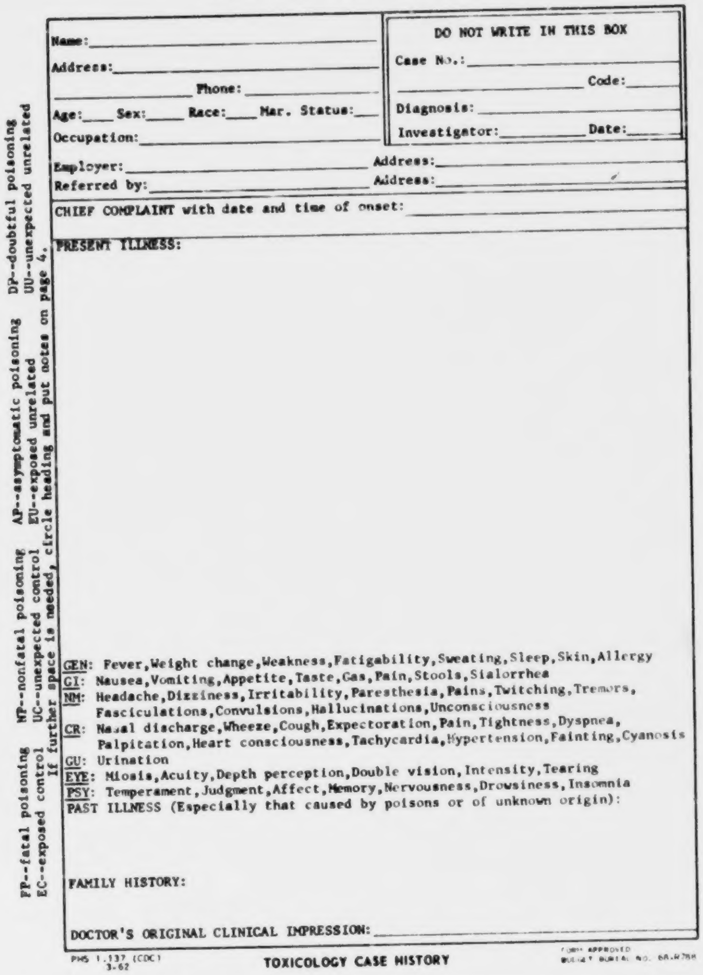
Treatment: If the eyes or skin are contaminated, they should be thoroughly washed. Two percent butyn sulfate ophthalmic ointment may be placed in the eyes immediately after washing to allay pain;

later cortisone ophthalmic ointment may be used to reduce inflammation. Any analgesic ointment may be applied to the skin.

If xylene has been taken by mouth, an effort should be made to remove it by induced vomiting and by gastric lavage. Oil laxatives should be avoided if the xylene served as a vehicle for an insecticide. Saline laxatives may be used. General care of the patient is symptomatic.

APPENDIX A

CASE HISTORY FORM*



DO NOT WRITE IN THIS BOX

Case No.: ______

______ Code: ______

Diagnosis: ______

Investigator: ______ Date: ______

Name: ______

Address: ______

______ Phone: ______

Age: ____ Sex: ____ Race: ____ Mar. Status: ____

Occupation: ______

Employer: ______ Address: ______

Referred by: ______ Address: ______

CHIEF COMPLAINT with date and time of onset: ______

PRESENT ILLNESS:

GEN: Fever, Weight change, Weakness, Fatigability, Sweating, Sleep, Skin, Allergy

GI: Nausea, Vomiting, Appetite, Taste, Gas, Pain, Stools, Sialorrhea

NM: Headache, Dizziness, Irritability, Paresthesia, Pains, Twitching, Tremors, Fasciculations, Convulsions, Hallucinations, Unconsciousness

CR: Nasal discharge, Wheeze, Cough, Expectoration, Pain, Tightness, Dyspnea, Palpitation, Heart consciousness, Tachycardia, Hypertension, Fainting, Cyanosis

GU: Urination

EYE: Miosis, Acuity, Depth perception, Double vision, Intensity, Tearing

PSY: Temperament, Judgment, Affect, Memory, Nervousness, Drowsiness, Insomnia

PAST ILLNESS (Especially that caused by poisons or of unknown origin):

FAMILY HISTORY:

DOCTOR'S ORIGINAL CLINICAL IMPRESSION: ______

FP--fatal poisoning NP--nonfatal poisoning AP--asymptomatic poisoning DP--doubtful poisoning

EC--exposed control UC--unexpected control EU--exposed unrelated UU--unexpected unrelated

If further space is needed, circle heading and put notes on page 4.

PHS 1.137 (CDC)
3-62

TOXICOLOGY CASE HISTORY

FORM APPROVED
BUDGET BUREAU NO. 68-R788

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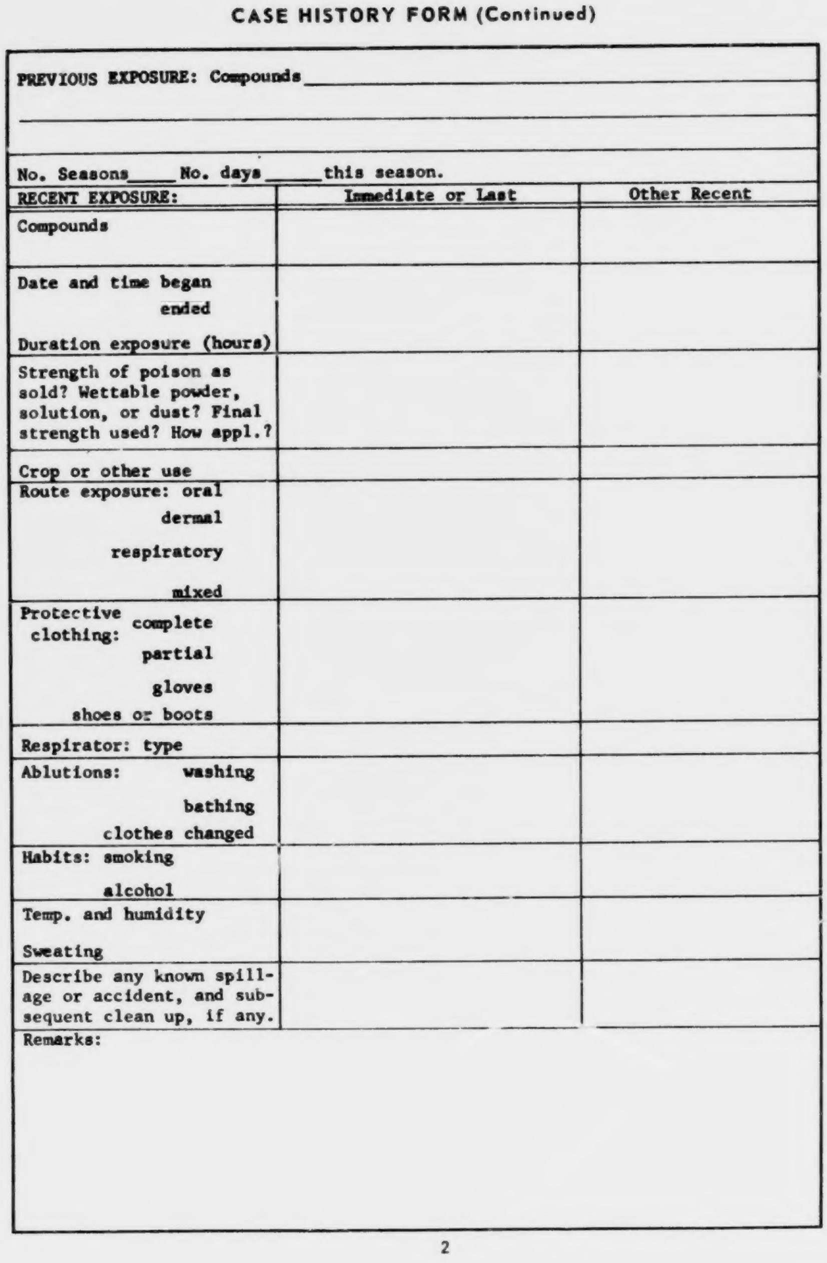
*The form is shown in reduced size. Full-sized copies will be sent to collaborating physicians who request them from the following addresses.

Communicable Disease Center
Atlanta 22, Georgia
Attn: Toxicology Section

U. S. Public Health Service
P. O. Box 73
Wenatchee, Washington

U. S. Public Health Service
4402 North Seventh Street
Phoenix 12, Arizona



CASE HISTORY FORM (Continued)

PREVIOUS EXPOSURE: Compounds____

No. Seasons_____No. days______this season.

RECENT EXPOSURE:	Immediate or Last	Other Recent
Compounds		
Date and time began ended Duration exposure (hours)		
Strength of poison as sold? Wettable powder, solution, or dust? Final strength used? How appl.?		
Crop or other use		
Route exposure: oral dermal respiratory mixed		
Protective clothing: complete partial gloves shoes or boots		
Respirator: type		
Ablutions: washing bathing clothes changed		
Habits: smoking alcohol		
Temp. and humidity Sweating		
Describe any known spillage or accident, and subsequent clean up, if any.		

Remarks:

2

CASE HISTORY FORM (Continued)

LABORATORY ANALYSES:

Lab No.	SAMPLE	DATE	HOUR	ANALYSIS FOR	RESULTS	BY

TREATMENT AND CLINICAL COURSE:

FIRST AID______________________________ by______________________

ATTENDED BY_________________________ M.D. of______________________
Address

Home, Office, Hospital____

ADMITTED: Date_______________ Hour______ Condition_________________

DISCHARGED: Date_________________ Condition______________________

DETAILS:

CONVALESCENCE RECOMMENDATIONS AND RETURN TO WORK:

APPENDIX B

Instructions for obtaining and shipping a fat biopsy for analysis for fat soluble compounds.

1. Fat from any portion of the body is suitable. However, when performing an operation primarily for the purpose of obtaining a biopsy, it is convenient to obtain the fat from the subcutaneous tissue of the anterior part of the abdomen. It is more comfortable for the patient if the belt line is avoided for the site of incision. The minor surgical procedure may be done on an outpatient basis.

2. The amount of fat should be about 2.5 g. This is a piece about the size of the tip of a man's thumb. The fat should be separated from any attached skin or other nonfatty tissue, blotted with paper toweling, and then weighed carefully on a pharmacist's balance (or one more accurate).

3. Immediately after weighing, the biopsy should be placed into a small, wide-mouth bottle and frozen. No preservative should be used because of interference with certain tests, except that 10% formalin may be used if chlorinated hydrocarbons are the only compounds for which analysis is desired. The container should be tightly closed and taped and the label filled in with the following information:

(a) Name of patient

(b) Weight of sample in grams
(accurate to at least two decimal places)

(c) Date sample taken

(d) Name of referring physician

Frozen samples should be shipped in dry ice by air. Samples preserved with formalin may be shipped by surface mail. Specimens should be sent to the nearer of the following addresses:

Communicable Disease Center
Atlanta 22, Georgia
Attn: Toxicology Section

U. S. Public Health Service
P. O. Box 73
Wenatchee, Washington

APPENDIX C

Instructions for drawing, preparing, and shipping blood samples for cholinesterase determinations.

Blood should be taken by venipuncture in the usual way, using sterile equipment. Heparin is the anticoagulant of choice, and the minimal amount to prevent clotting should be used, so as to dilute the blood sample as little as possible. Merely wetting the inside of the syringe with heparin as supplied in the ampule (1,000 units per milliliter) is sufficient. Sodium citrate may be used if heparin is unavailable. The blood should be carefully transferred from the syringe to a clean, dry 15-ml. graduated centrifuge tube by gentle pressure on the plunger. The needle should be removed, and the aperture of the syringe should be placed in contact with the side of the tube before the blood is forced out. These precautions are helpful in preventing hemolysis. Ideally, ten milliliters of blood should be drawn and processed to insure adequate amounts of material for cholinesterase analysis and other tests that may be indicated.

The collected blood is centrifuged for 15 minutes at 2,000 rpm, and the plasma thus separated. The plasma may now be placed in a clean, dry, glass or polyethylene test tube of suitable size, closed with a tight-fitting, rubber or polyethylene stopper, and plainly labeled. The white cells and any remaining plasma at the interface in the centrifuge tube are discarded. The remaining red cells are transferred to a test tube, stoppered, and labeled in a manner similar to that suggested for plasma.

The samples must be kept refrigerated. For shipment, the tubes should be wrapped to prevent breakage. Refrigeration may be provided by placing the samples between plastic bags filled with chips of ice. Refrigeration may also be provided by "refreezants" (water or silica gel packaged in plastic or metal) sold for keeping picnic lunches and drinks cold. Before use, refreezants must be thoroughly frozen.

It is just as important that the shipping containers be carefully insulated and sealed as that the samples be surrounded by ice.

Never use dry ice for cholinesterase samples because the samples will freeze and the red cell sample will be ruined.

It is recommended that shipments be made by the fastest available means of transportation in order to insure adequate refrigeration for the samples during the entire period of shipment. Please mark all packages **"PERISHABLE," "RUSH,"** and **"REFRIGERATE UPON ARRIVAL – DO NOT FREEZE."**

Samples for analysis should be sent to the closest of the following laboratories:

Communicable Disease Center
Atlanta 22, Georgia
Attn: Toxicology Section

U. S. Public Health Service
P. O. Box 73
Wenatchee, Washington

U. S. Public Health Service
4402 North Seventh Street
Phoenix 12, Arizona

APPENDIX D

Instructions for shipping stomach contents, urine, tissues, or certain other materials for toxicological examination.

If the nature of the toxicant is unknown, it may be expedient to do a bioassay, and formalin or other preservatives (even volatile ones) may interfere with the procedure. In such instances, specimens for routine toxicological study may be frozen and shipped with dry ice. Packages should be marked **"PERISHABLE," "RUSH,"** and **"FREEZE ON ARRIVAL."** They should be shipped by the fastest means of transportation available to one of the addresses given below.

Each sample of an organ or tissue should be in a separate jar.

It is usually satisfactory to preserve urine with a few drops of 10% formalin and ship the specimen by ordinary mail. In case of doubt, urine too may be shipped under refrigeration. (Of course, liquid in glass cannot be shipped with dry ice because freezing of the liquid may break the glass.)

Samples of insecticides suspected of being the cause of poisoning should be shipped in a completely separate package from blood, tissue, or other biological specimens because of the possibility of vapor contamination. If clothing or other objects suspected of being contaminated by insecticides are to be shipped, they should be put in a third package; if there is any possible difference between the samples, they should be sealed in glass jars. Ordinary plastic wrapping may not be sufficient to prevent cross-contamination.

Communicable Disease Center
Atlanta 22, Georgia
Attn: Toxicology Section

U. S. Public Health Service
P. O. Box 73
Wenatchee, Washington

APPENDIX E

ARTIFICIAL RESPIRATION

Unless the apneic victim is in a toxic atmosphere, do not waste time moving him. Start artificial respiration at once. The mouth-to-mouth (or mouth-to-nose) technique of artificial respiration is the only one that requires no equipment and will still overcome the airway resistance that may be present in poisoning by organic phosphorus insecticides as a result of bronchial constriction and excessive secretion. No matter why breathing has stopped, this technique allows the rescuer to get a better idea of the volume and pressure needed to inflate the victim's lungs than can be gotten by other methods. Timing tends to be correct automatically with the mouth-to-mouth method, because the nonbreathing adult needs about the same volume of air as the rescuer breathes at the normal rate (12 to 16 per minute), while the infant or very young child requires a smaller volume delivered at a slightly higher rate (about 20 per minute).

When a person is unconscious and stops breathing, the base of the tongue tends to press against the back of the pharynx and block the passage of air from either the nose or mouth into the lungs. To clear the upper airway, wipe out the mouth with your finger covered by your handkerchief or your shirt. Roll the victim onto his back. Place both your hands at the angles of his lower jaw and lift it so that it juts out and the head tilts back (Fig. 1). You may do the same thing by putting your thumb in his mouth, grasping the jaw, and pulling it forward.

Having cleared the airway, pinch the victim's finger so that your fingernail is driven in hard enough to cause sharp pain in a normal person. This may cause the victim to gasp and start breathing again. If this maneuver fails and if the victim is a child, place your mouth over his mouth and nose and blow into him gently so that the chest is inflated to about the normal degree (Fig. 2). Remove your mouth to take fresh air and to let the victim breath out. As you remove your mouth, turn your ear to listen for air being passively exhaled by the victim. Repeat the active inflation and passive deflation of the victim 20 times per minute.

If the victim is adult, place your mouth over either his nose or mouth and pinch the other opening closed with the fingers of one hand. (You can blow between his teeth even though his jaws are closed.) You will have to blow harder to get enough air into an adult, especially a heavily muscled one. Insofar as possible, keep the jaw jutting out while artificial respiration progresses.

If there seems to be resistance to your blowing, recheck the position of the jaw. A child may be held up by the ankles (Fig. 3) or hung with his abdomen over one of your arms (Fig. 4) while you pat him sharply on the back in the hope of dislodging any obstructing matter. This effort should last only a moment. Wipe out the mouth again and continue artificial respiration.

If obstruction is still present after the jaw has been rechecked and if the victim is too heavy to lift, he may be rolled onto his side and struck several times between the shoulder blades in the hope of dislodging foreign matter. Clean out the mouth and continue artificial respiration.

If the victim vomits, turn the head quickly to the side. Clear out the mouth and continue artificial respiration as soon as possible. Those who do not wish to contact the victim directly may cover his mouth with a cloth. This will not interfere very much with the exchange of air.

If someone comes to help, send him to call the police for an ambulance equipped for mechanical artificial respiration.

If the victim begins to breathe for himself, try to time your blowing to match his rate of breathing and help his natural inspiration. As his breathing becomes stronger, stop helping but watch very closely lest he stop again. Keep the person as quiet as possible.

If the victim does not start to breath promptly, do not despair. Remember that some poisoned people who required artificial respiration for **many hours** survived without permanent injury.

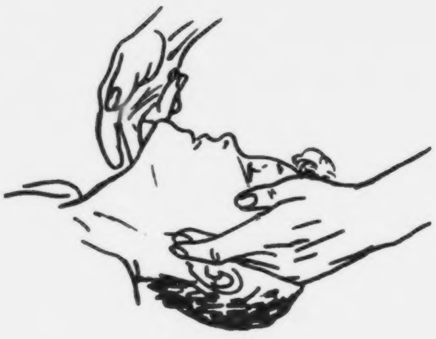


FIGURE 1. Tilt the head back and lift the jaw forward before giving artificial respiration.

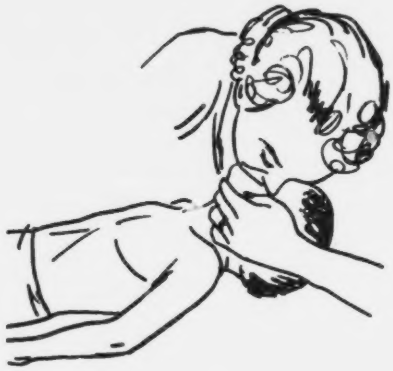


FIGURE 2. Blow into the child's mouth and nose about 20 times a minute (12-16 for adults) holding the head back and the chin up.

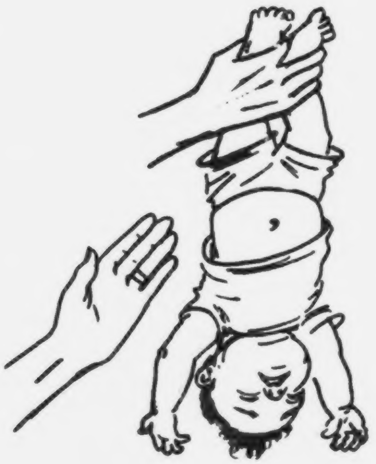


FIGURE 3. Invert the infant and pat him on the back if there is something caught in the windpipe.

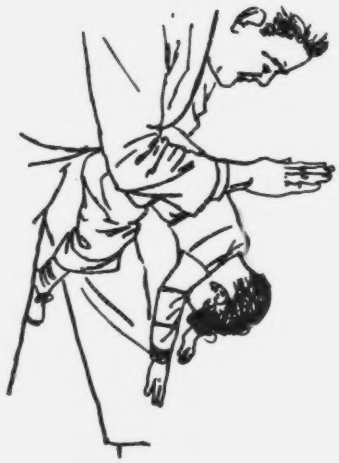


FIGURE 4. Hold an older child over your arm to dislodge an obstruction to breathing.

Figures on artificial respiration by courtesy of the American Red Cross.

SUMMARY

1. Don't waste time moving the victim unless he is actually in a toxic atmosphere.
2. Quickly clear the mouth and throat.
3. Tilt head back as far as possible.
4. Lift lower jaw forward.
5. Pinch the patient sharply to see if he will gasp and breathe. If this fails,
6. open your mouth wide and blow into the victim's mouth and nose (or one of them with the other squeezed shut) until you see the chest rise.
7. Listen for exhalation.
8. Repeat (No. 6 and 7) 12 to 16 times per minute for adults or 20 per minute for small children.

LIST OF MANUFACTURERS

1. Agricultural Chemical Company, Phoenix, Arizona.
2. Amchem Products, Inc., Agricultural Chemicals Division, Ambler, Pennsylvania.
3. American Cyanamid Company, Agricultural Chemicals Division, 30 Rockefeller Plaza, New York 20, New York.
4. American Potash and Chemical Corporation, Agricultural Chemicals Division, 3000 West 6th Street, Los Angeles 54, California.
5. Bayer Farbenfabriken, Bayerwork, Leverkusen, Germany.
6. California Chemical Company, Ortho Division, Lucas and Ortho Way, Richmond, California.
7. Chemagro Corporation, Hawthorn Road, Kansas City 20, Missouri.
8. Chipman Chemical Company, Bound Brook, New Jersey.
9. Ciba, Ltd., Basel, Switzerland.
10. Commercial Solvents Corporation, 260 Madison Avenue, New York 16, New York.
11. Dow Chemical Company, Midland, Michigan.
12. E. I. du Pont de Nemours and Company, Inc., Grasselli Chemicals Department, Wilmington 98, Delaware.
13. Fisons Pest Control Ltd., Harston, Cambridge, England.
14. Geigy Agricultural Chemicals, Post Office Box 430, Yonkers, New York.
15. Hercules Powder Company, Inc., Agricultural Chemicals Division, Wilmington 99, Delaware.
16. Imperial Chemicals Industries Ltd., Curzon Street, London W1, England.
17. Monsanto Chemicals Company, Organics Division, 800 North Lindberg Blvd., St. Louis 24, Missouri.
18. Montecatini, Via F. Turati 18, Milan, Italy..
19. Motomco, Inc., 89 Terminal Avenue, Clark, New Jersey.
20. Norda Essential Oil and Chemical Company, 601 West 26th Street, New York, New York.

21. Rohm and Haas Company, Washington Square, Philadelphia 5, Pennsylvania.
22. Shell Chemical Corporation, Agricultural Chemicals Division, 110 West 51st Street, New York 20, New York.
23. Standard Agricultural Chemicals, Inc., Hoboken, New Jersey.
24. Stauffer Chemical Company, 380 Madison Avenue, New York 17, New York.
25. Thompson Hayward Chemical Company, Kansas City, Missouri.
26. Union Carbide Chemicals Company, 30 East 42nd Street, New York 17, New York.
27. Velsicol Chemical Corporation, 330 East Grand Avenue, Chicago 11, Illinois.

Names and addresses of manufacturers whose trade name products are mentioned in this Handbook are provided for the convenience of the physician. Manufacturers are often good sources of recent and detailed information on the toxicology of their products. It may sometimes be necessary for a physician to get in touch with one of them without delay.

INDEX

Insofar as possible, common or standard names have been used in the text of this Handbook. However, some containers for pesticides are so labeled that only the chemical name or the trade name of the principal active ingredient is given. Chemical names and important trade names of compounds mentioned in the text are listed in the following index so the Handbook will be of use to physicians in emergencies. In most instances, the form of chemical name favored by *Chemical Abstracts* has been used. Unfortunately, limitation of space makes it impossible to include all relevant trade names or all important variants of chemical names. A number associated with each trade name below indicates a company in the preceding list that is concerned. Main headings in the text are printed in bold type in the index.

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U. S. GOVERNMENT PRINTING OFFICE: 1963 O - 689679